



ORIGINAL RESEARCH PAPER

Pulmonary Medicine

PROPORTION OF MDR-TB IN CAT-II FAILURES AND ITS RELATIONSHIP WITH TYPE OF PATIENT

KEY WORDS: MDR-TB, Cat.II failures,

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ABSTRACT

Introduction: Patients whose sputum smears remains positive at the end of intensive phase of three months, treatment with R, H, Z and E is extended for one more month. After four months patients are shifted to continuation phase, irrespective of their sputum status. It is thought that, a large number of those positive patient even after four months of CAT-II would imply drug resistance of which MDR would be more likely. Present research was designed to study the proportion of MDR-TB in CAT-II failures and its relationship with type of patient.

Aim & Objectives: To study the proportion of MDR-TB in CAT-II failures and its relationship with type of patient.

Material & Methods: Prospective study of patients registered on CAT-II from December 2006 to, November 2007, at L. R. S. Institute New Delhi.

Results: Of the 272 smear-positive patients registered to CAT-II regimen 184 (67.6%) had a successful treatment outcome (cured), 49 (18%) defaulted, and 24 (8.8%) patients failed to CAT-II treatment. The cure rate amongst 'Relapse' cases was 68.6%, amongst 'TAD' 67% and 70% amongst 'Failure'. The failure rate amongst 'Relapse' cases was 11.3%, in comparison to 'TAD' (5.7%) (p value.003). 41 (15%) patients were sputum smear positive at four month or more. culture could be performed in only 31(75.6%). Among 31 cases (16 'Relapse', 13 'TAD' and 2 'CAT-I Failure' cases) 12 (38.7%) had MDR-TB, 3 (9.6%) were resistant to Isoniazid (H) only, 5(16.1%) were sensitive to all drugs and there was no growth in the culture for 11 (35.4%) patients. Among 16 'Relapse' patients, 6 (37.5%) were MDR-TB, 6 (37.5%) were culture negative, 2 (12.5%) were resistant to Isoniazid (H) only, and 2 (12.5%) patients were sensitive to all drugs. Among 13 'TAD' patients, 4 (30.7%) were MDR-TB, 5 (38.4%) were culture negative, 1 (7.69%) was resistant to Isoniazid (H) only, and 3 (23%) patients were sensitive to all drugs. Among 2 Cat-I Failure patients, both (100%) were MDR-TB.

Conclusion: Failure was observed among 8.8% of patients and MDR-TB was 52% among Category II failures. Only 2 of 17 Cat.I Failure patients (11.7%) were MDR-TB and hence, giving Cat.II regimen to this group would be the appropriate treatment option. This study also shows that Category II regimen may be adequate for re-treatment cases except for the drug resistant TB patients.

INTRODUCTION

Tuberculosis (TB) is a major cause of illness and death worldwide. Globally, 9.27 million new cases and 1.77 million deaths from TB occurred in 2007. A total of 564131 patients were re-treated under DOTS in 2006. The re-treatment success rate in 2006 was 70%.¹ Adding to the threat of tuberculosis is the emergence of multidrug-resistant tuberculosis (MDR), i.e., resistance to at least Isoniazid and Rifampicin. There were an estimated 511000 cases of multidrug-resistant TB (MDR-TB) in 2007. Of these, 289 000 were among new cases (3.1% of all new cases) and 221000 were among cases that had been previously treated for TB (19% of all previously treated cases). Of the 511000 incident cases of MDR-TB in 2007, 349000 (68%) were smear-positive (including new + previously treated).¹

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. Expansion of DOTS services took place on a larger scale in India from 1997. RNTCP has been remarkably successful and has achieved high cure rates of 86% nationally in new smear positive cases. For previously treated patients excluding others, the success rate to the re-treatment regimen (CAT-II) was 70.4%. Available data from the earlier district-wise and now state representative surveys in Gujarat and Maharashtra have found ~3% MDR-TB among new cases and 12–17% among cases with a previous history of anti-TB treatment.²

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 (2SHRZE3/

1EHRZ3/5HRE3) given three times a week, throughout the 8 months period. Patients whose sputum smears remains positive at the end of intensive phase of three months, treatment with R, H, Z and E is extended for one more month. After four months patients are shifted to continuation phase, irrespective of their sputum status.

It is thought that, a large no. of those positive even after four months of CAT-II would imply drug resistance of which MDR would be more likely. Present research was designed to study the proportion of MDR-TB in CAT-II failures and its relationship with type of patient.

MATERIALS AND METHODS

Study design

This was a prospective study to measure the rate and pattern of drug resistance among patients who remained sputum positive at 4th month or later, of CAT II treatment, under RNTCP.

Study area and population

The study was conducted in LRS Institute of TB and Respiratory Diseases, New Delhi, in North India. The study area has 11 designated microscopy centres and 15 DOTS centers, covering a population of approx. 1000000. Smear positive patients, with history of previous anti-tuberculosis treatment for more than one month, comprising cases of 'Relapse' Treatment after Default ('TAD'), and 'Failure' started on the CAT-II regimen from Dec.2006 to Nov.2007, constituted the study population.

Data collection

Symptomatic patients visited to any of the DOTS centre were screened by examination of three sputum smears for acid-fast

bacilli (AFB) (Ziehl-Neelsen method). Diagnosis, treatment and monitoring were done according to RNTCP guidelines. The patients positive at 4th month or later on of cat II treatment were advised to provide early morning sputum specimens. The sputum samples were processed for culture and drug sensitivity testing by BACTEC method at the LRS institute mycobacteriology laboratory. The sputum sample was put up for culture on BACTEC 12B medium. Drug sensitivity testing was carried out for INH, Rifampicin, Streptomycin and Ethambutol using the Modified 1% proportional method.

Statistical analysis

Pearson's Chi-square test of significance was performed to test the difference between different proportions, P values <0.05 were considered as significant. Chi-square goodness of fit test was performed to test the difference between frequencies.

RESULTS

From December 2006 to, November 2007, a total of 272 smear-positive patients were started on re-treatment with CAT-II regimen. These 272 patients included – 115 (42%) cases of 'Relapse', 139 (51%) 'TAD', 17 (6 %) 'CAT-I Failure' and 1 (0.3%) 'CAT-II Failure' cases. Out of these 272 patients 41 (15%) patients were sputum smear positive at four month or more. Proportionately, it was 18.2 % (21 of 115) amongst Relapses, 12.2% (17 of 139) amongst TAD, 11.7% (2of 17) amongst the Cat-I Failures and 100% (1 of 1) amongst the Cat-II Failures.

Of the 41 patients who remained sputum smear positive at four month or more of treatment, culture could be performed in only 31 (75.6%). These 31 patients included -16 cases of 'Relapse', 13 'TAD' and 2 'CAT-I Failure' cases. In remaining 10 patients, 4 patients defaulted before processing for culture and sensitivity, 3 patients refused for culture and sensitivity and failed on CAT II later on, 2 patients had only 4 bacilli in sputum smear and cured on CAT II later on and one patient died before processing for culture and sensitivity.

Drug susceptibility profile among patients with positive smear during treatment (table 1)

Out of 31 patients in which culture were performed, 11 (35%) were culture negative whereas 20 (65%) cases were culture positive (p value 0.07). Out of 20 culture positive patients, proportion of resistance to any drug was significantly higher (75%) than sensitive to all drugs (25%); (p value 0.02). Among 31 cases, 12 (38.7%) had MDR-TB, 3 (9.6%) were resistant to Isoniazid (H) only, 5(16.1%) were sensitive to all drugs and there was no growth in the culture for 11 (35.4%) patients. Among 16 'Relapse' patients, 6 (37.5%) were MDR-TB, 6 (37.5%) were culture negative, 2 (12.5%) were resistant to Isoniazid (H) only, and 2 (12.5%) patients were sensitive to all drugs. Among 13 'TAD' patients, 4 (30.7%) were MDR-TB, 5 (38.4%) were culture negative, 1 (7.69%) patient was resistant to Isoniazid (H) only, and 3 (23%) patients were sensitive to all drugs. Among 2 Cat-I Failure patients, both (100%) were MDR-TB.

Table 1. Drug susceptibility profile among patients with positive smear during treatment

| Type of Patient | No. | Positive at 4 Month / More | Culture Done | MDR-TB | Mono H Resistant | Pan Sensitive | Culture Negative |
|-----------------|-----|----------------------------|--------------|------------|------------------|---------------|------------------|
| Relapse | 115 | 21 (18.2%) | 16 | 6 (37.5%) | 2 (12.5%) | 2 (12.5%) | 6 (37.5%) |
| Tad | 139 | 17 (12.2%) | 13 | 4 (30.7%) | 1 (7.69%) | 3 (23%) | 5 (38.4%) |
| Cat-i failure | 17 | 2 (11.7%) | 2 | 2 (100%) | - | - | - |
| Cat-ii failure | 1 | 1 | - | - | - | - | - |
| Total | 272 | 41 (15%) | 31 | 12 (38.7%) | 3 (9.6%) | 5 (16.1%) | 11 (34.3%) |

* H-Isoniazid,TAD- Treatment After Default

Treatment outcome according to 'type' of cases (Table 2)

Of the 272 smear-positive patients registered to CAT-II regimen 184 (67.6%) had a successful treatment outcome (cured), 49 (18%) defaulted, and 24 (8.8%) patients failed to CAT-II treatment.

The cure rate amongst 'Relapse' cases was 68.6%, amongst 'TAD' 67% and 70% amongst 'Failure'. The failure rate amongst 'Relapse' cases was 11.3%, in comparison to 'TAD' (5.7%) (p value.003). 14 (5%) patients died during the course of the treatment.

Table 2. Treatment outcome according to 'type' of cases

| Type of patient | No. | Cured | Failed | Defaulted | Expired | T-out |
|-----------------|-----|-------------|------------|-----------|----------|-----------|
| Relapse | 115 | 79 (68.6%) | 13 (11.3%) | 15 (13%) | 8 (7%) | - |
| Tad | 139 | 93 (67%) | 8 (5.7%) | 32 (23%) | 6 (4.3%) | - |
| Cat-i failure | 17 | 12 (70%) | 2 (11.7%) | 2 (11.7%) | - | 1 (5.8%) |
| Cat-ii failure | 1 | - | 1 (100%) | - | - | - |
| Total | 272 | 184 (67.6%) | 24 (8.8%) | 49 (18%) | 14 (5%) | 1 (0.36%) |

*T-out-Transfer out, TAD- Treatment After Default

Response to CAT-II treatment versus drug susceptibility pattern (table 3 & 4)

Out of 31 patients in which culture were performed 21 (67.7%) failed to treatment, 5(16%) patients declared cured, 3(9.6%) patients defaulted and 2 (6.4%) patients expired during treatment.

Failure rate in culture positive patients was significantly higher (95%) in comparison to culture negatives (18%); (p value <0.001). Failure rate in cases with resistance to any drug was significantly higher (93%) in comparison to culture negatives (18%); (p value 0.002). 11 of 12 (91%) MDR-TB patients, 5 of 5 PANSENSITIVE (100%), 3 of 3 MONO H RESISTANT (100%) failed to treatment whereas, only 2 (18%) of CULTURE NEGATIVE patients failed to treatment (p value 0.011).

Table 3. Response to CAT-II treatment versus drug susceptibility pattern

| Culture report | No. | Cured | Failed | Defaulted | Expired |
|------------------|-----|-------|--------|-----------|---------|
| MDR-TB | 12 | - | 11 | - | 1 |
| Mono H resistant | 3 | - | 3 | - | - |
| Pan sensitive | 5 | - | 5 | - | - |
| Culture negative | 11 | 5 | 2 | 3 | 1 |
| Total | 31 | 5 | 21 | 3 | 2 |

Table 4. Drug susceptibility pattern

| Drug susceptibility pattern | No. |
|-----------------------------|-----|
| Culture negatives | 11 |
| Culture positives | 20 |
| Pan-sensitive | 5 |

| | |
|------------------------|----|
| Resistance to any drug | 15 |
| ANY RESISTANCE | |
| Any H resistance | 15 |
| Any R resistance | 12 |
| Any E resistance | 2 |
| Any S resistance | 4 |
| MONO RESISTANCE | |
| Mono H resistance | 3 |
| MULTIDRUG RESISTANCE | 12 |
| H+R | 8 |
| H+R+S | 2 |
| H+R+E+S | 2 |

*H-Isoniazid, R-Rifampicin, E-Ethambutol, S-Streptomycin

DISCUSSION

In this study, for previously treated patients excluding others, the success rate was (68.6%), which is almost equal to national success rate to the re-treatment regimen (CAT-II). The cure rate amongst 'Relapse' cases was 68.6%, amongst 'TAD' 67% and 70% amongst 'Failure'. In our study the failure rate of re-treatment regimen was 8.8%. In a retrospective study Gninafon et al,³ from Cotonou, Benin, has reported satisfactory success rates among re-treatment patients (78%). The success rate was similar among relapses (80%) and failures (85%). The failure rate for all retreatment patients was low (3%).

In our study proportion of MDR-TB

- Amongst retreatment cases : 4.4%
- Amongst pos. at 4 month/ more : 38.7%
- Amongst CAT II Failure : 52%
- Amongst culture positives : 60%
- Amongst resistant to any drug : 80%

Amongst MDR-TB, 2 drug resistance (H+R) pattern was significantly higher (75%) than, 3 drug resistance (H+R+S) and 4 drug resistance (H+R+E+S) pattern ; (p value 0.007).

In any drug resistance, resistance to H was commonest (45.45%), followed by resistance to R (36.36%), resistance to S (12%) and resistance to E (6%). In a study done by Pauline Joseph et al⁴, 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. Mohamed Shafiq et al⁵, found the possibility of having MDR TB to be very high to the tune of 86.66% when a patient fails with Cat II under RNTCP.

In our study the failure rate amongst 'Relapse' cases was significantly higher (11.3%), in comparison to 'TAD' (5.7%) (p value.003). In a study done by Dhingra et al⁶, Category II regimen was observed to have significantly higher unfavorable outcome in "failure group" as compared to "relapse group".

In our study proportion of MDR-TB amongst pos. at 4 month/ more was higher in Relapses (37.5%) than, TAD (30.7%) though not significant; (p value 0.0625). Only 2 (11.7%) of 17 CAT-I Failure cases failed on CAT-II regimen. Though both of them were MDR-TB but, significance could not be commented because of small sample size. In a study conducted by Jasmin Johnson et Al⁷, treatment default was found to be most important factor associated with drug resistance.

LIMITATIONS

Culture and drug susceptibility pattern of patients before starting CAT II treatment were not available. Patients proven to be Non-MDR i.e. mono-resistant, pansensitive and culture negative declared as failure after completion of CAT II, were not confirmed as failure of treatment by culture. This issue is important because the smear positivity could be due to excretion of dead bacilli in these patients.

CONCLUSIONS

Failure was observed among 8.8% of patients. There were 52%MDR-TB cases and 48% cases were mono-resistant, pan

sensitive and culture negatives among failed cases. Only 2 of 17 Cat.I Failure patients (11.7%) were MDR-TB and hence, giving Cat.II regimen to this group would be the appropriate treatment option.

This study also shows that Category II regimen may be adequate for re-treatment cases except for the drug resistant TB patients. DST should be done for patients who remain sputum smear positive during the retreatment period and appropriate regimens should be started as early as possible for better treatment outcome and to reduce transmission of drug resistant TB.

REFERENCES

1. Global tuberculosis control: Epidemiology, Strategy, financing: WHO report 2009. WHO/HTM/TB/2009.411.
2. Central TB Division, Directorate General of Health Services, Ministry of Health and Family Welfare: TB India 2009 – RNTCP Status Report.
3. M. Gninafon, L. Tawo, F. Kassa, G. P. Monteiro, J-P. Zellweger, H. Shang, et al. Outcome of tuberculosis retreatment in routine conditions in Cotonou, Benin. *Int.J. tuberc Lung Dis* 2004; 8(10): 1242-1247.
4. Pauline Joseph, V. Chandrasekaran, A. Thomas, P.G. Gopi, R. Rajeswari, R. Balasubramanian, et al. Influence of Drug Susceptibility on Treatment Outcome and Susceptibility Profile of 'Failures' to Category II Regimen. *Indian J Tuberc* 2006; 53:141-148.
5. Mohamed Shafiq, R. Atharunnisa Begum, R.Sridhar. Drug resistance profile among post-Cat II sputum positive patients - critical analysis. *Indian J Tuberc* 2006; 53:166
6. V.K. Dhingra, S. Rajpal, N. Aggarwal, J.K. Aggarwal. Treatment outcome of Category II regimen in "Failure" and "Relapse" sub-groups and their follow-up. *Indian J Tuberc* 2006; 53:55
7. Johnson J, Kagal A, Bharadwaj R. Factors associated with drug resistance in pulmonary Tuberculosis. *Indian J chest Dis Allied Sci* 2003; 45: 105-9.