ORIGINAL ARTICLE

Frequency of Drug Resistance Among Retreatment Tuberculosis Patients in Gulab Devi Chest Hospital

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ABSTRACT

Objective: Emerging drug resistance is a global challenge. Efforts are underway to detect and treat this menace. We carried out this study to ascertain the frequency of MDR among Category-II pulmonary TB patients.

Methodology: In this cross-sectional descriptive study all MTB detected cases admitted in hospital OR being referred in OPD were included in the study. CAT-II cases subjected to GeneXpert analysis to detect MDR in terms of Rifampicin resistance. Including basic demographic details all the data were recorded in a short structured questionnaire.

Results: A total of 1085 MTB detected patients were included in this study. There was an overall male predominance (53%). Majority of our patients were in the range of 15-45 years of age. Out of 1085 patients Category-II treated patients were accounting 38% (411) of the total MTB cases. Rifampicin resistance was detected in 211 (54%) cases of the total Category-II treated patients.

Conclusion: Over all frequency of MDR in Category-II treated patients was 54%. Primary drug resistance was a strong risk factor for failure and relapse and for acquiring further resistance. As 59% of failure cases had RIF resistance, the standard re-treatment regimen appears inadequate for failure cases.

Keywords: Multiple drug resistance, Category-II treatment, Failure cases, Retreatment regimen.

INTRODUCTION

Tuberculosis is among the most serious infectious causes of global morbidity and mortality.[1,2] Each year, more than 8 million people get tuberculosis disease, and 1.8 million die from tuberculosis.[3, 4] Adding to the threat of tuberculosis is the emergence of multidrug resistant tuberculosis (MDR), i.e., resistance to at least isoniazid and rifampicin.[5, 6] Treatment results of MDR tuberculosis using the World Health Organization (WHO) standard regimens tend to be poor; [7, 8] much better treatment results can be obtained with individualized regimens, provided defaulting from treatment can be prevented by intensive follow up.[9, 10] Patients who fail or relapse are usually given one of the standard WHO re-treatment regimens.[11] There have been concerns that the WHO retreatment regimen could be exacerbating the MDR-TB problem. Therefore the WHO has considered a strategy of supervised treatment of MDR-TB cases, the so called 'DOTS-plus' programme, to try to contain the problem.[12] The WHO is carefully vetting DOTS plus applications and monitoring them where they are implemented. We also stress the importance of continuous monitoring of drug resistance trends. Considering previous anti-tuberculosis therapy as the most important risk factor for the development of MDR TB the present study aims to determine the frequency of drug resistance among failure and relapse cases in Category-II treated patients.

MATERIALS AND METHODS

Design & Setting: A cross sectional study of 1139 patients was carried out in Gulab Devi chest hospital, Lahore between January 2012 & December 2012.

Sample selection & Data collection: All MTB detected cases admitted in hospital or being referred as OPD patients were included in the study while those patients that were having ATT outside the DOTS and those having extrapulmonary tuberculous involvement were excluded. All cases were screened for HIV testing. Category-II cases subjected to GeneXpert analysis. The data depends all the parameters addressed in GeneXpert form filled by the referring personal. Patients found to be MTB detected and RIF resistance detected on GeneXpert, were later subjected to DST. Including basic demographic details all the data were noted on a short structured questionnaire.

Statistical Analyses: Analyses were done in Statistical Package for Social Sciences (SPSS)

version 16.0 and MS Excel. Qualitative data were presented in form of percentages and graphs while descriptive and frequency distribution was used for quantitative analyses.

RESULTS

A total of 1085 patients were included in this study. Basic demographic details of our patients are summarized in Table-1. Mean age of our patient was 39.7 ± 10.6 years. The overall M:F ratio in our series was 1.3:1 (618 vs. 467). Majority of our patients were in the range of 15-45 years of age.

Table-1: Basic Demographic Characteristics

	Frequency (N = 1085)	Percentage
Gender		
Males	618	57%
Females	467	43%
Age Groups		
Below 15 years	43	04%
15-45 years	759	70%
More than 45 years	283	26%

In these 1085 MTB detected cases the proportion of different treatment categories (along with Rifampicin resistance population in Category-II) is shown in FIG.01.

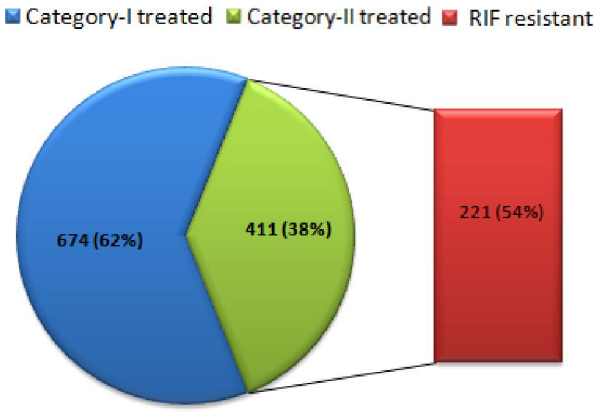

FIG.01-FREQUENCY OF DIFFERENT TREATMENT CATEGORIES IN MTB DETECTED CASES

There were 674 (62%) cases of Category-I treated patients and 411 (38%) cases of Category-II treated patients. Out of these 411 cases of Category-II RIF resistant was detected in 211 (54%).

FIG-02 shows frequency of RIF resistance in different types of cases in patients treated with Category-II regimen. There were 175 failure cases under Category-II treatment. RIF resistance was seen in majority of the failure cases (59%). Out of total relapse cases (117) RIF resistance was detected in 62 (53%) cases while only a minor proportion (36%) of default cases were RIF resistant.

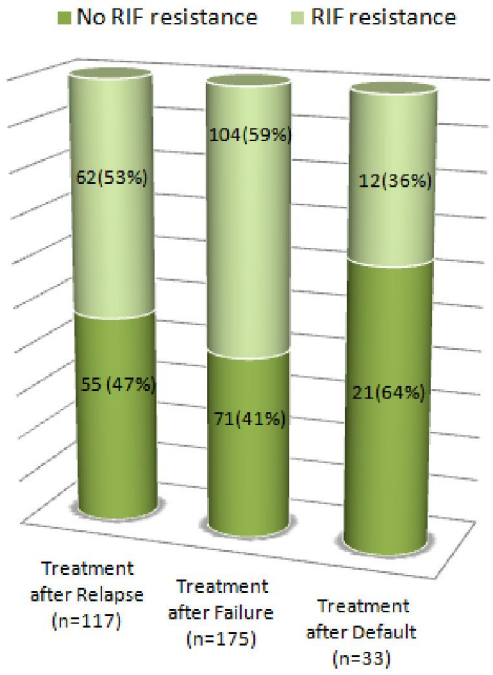

FIG.02-FREQUENCY OF RIF RESISTANCE IN DIFFERENT TYPES OF CASES

DISCUSSION

The molecular basis of MDR is now predominantly understood.[13, 14] Resistance to rifampicin is nearly always due to point mutations in the *rpo* gene in the beta subunit of DNA dependent RNA polymerase.[15] These mutations are not directly connected, and so separate mutations are required for organisms to change from a drug susceptible isolate to MDR-TB. In our study the patients found to be MTB detected and RIF resistance detected on GeneXpert, were later subjected to DST as the accurate diagnosis of MDR-TB requires a positive culture of *Mycobacterium tuberculosis* and drug susceptibility testing (DST). Genetic probes which detect drug resistance to rifampicin with > 95% accuracy are very suggestive of MDR-TB; <10% of rifampicin resistance is monoresistant, and so rifampicin resistance is a marker for MDR-TB in >90% of cases.[16]

Understanding the scientific basis of short course 6 month chemotherapy for tuberculosis

helps to explain why the loss of sensitivity to both isoniazid and rifampicin, even without resistance to additional drugs, has such major effects on outcome. Rifampicin is the best sterilizing drug, and monoresistance to this drug requires treatment with other drugs.[17] Numerous controlled trials have shown that a 6 month regimen of rifampicin and isoniazid, supplemented by pyrazinamide and streptomycin or ethambutol for the first 2 months, will provide a cure in >95% of cases if the medication is taken correctly. Such a regimen also renders infectious cases non-infectious in 2 weeks.[18]

Previous drug treatment is the largest single risk factor for the presence of MDR-TB.[19] As this study has also shown that failure cases on category-II treatment had a high prevalence of MDR (59%), approximately half of which was primary drug resistance and half was acquired. Among relapse cases, MDR was found in 53% of the total relapse cases. In an international comparative study, the rates of resistance in England and Wales in 1995 and 1997 were 6.9-7.2% for isoniazid resistance and 0.9-1.1% for MDR-TB for all patients, but 22-33% and 13-17%, respectively, for those patients with a history of prior treatment.[5] Therefore physicians should suspect that any patient with a prior treatment history, or failure during treatment, could have acquired resistance. The finding that failure was strongly associated with multi drug resistance is likely to apply to other excellent tuberculosis programmes.[20, 21] Urgent gene probes for rifampicin resistance should be carried out (as done in our patients) on material which is either microscopy or culture positive. A large multi centric study involving patients recruited at primary care level from different parts of the country is needed to determine the nationwide prevalence of MDR-TB in Category-II TB patients.

CONCLUSION

Over all frequency of MDR in Category-II treated patients was 54%. Primary drug resistance was a strong risk factor for failure and relapse and for acquiring further resistance. As 59% of failure cases had Rifampicin resistance, the standard re-treatment regimen appears inadequate for failure cases. In order to assess the efficacy of current interventions and their impact on the TB epidemic we stress the importance of continuous monitoring of drug resistance trends, we recommend that Rifampicin susceptible patients must be given an option for DST at the start of Category-II treatment.

REFERENCES

1. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. The Lancet. 1997;349(9061):1269-76.
2. Murray CJ, Lopez AD. Regional patterns of disability-free life expectancy and disability-adjusted life expectancy: global Burden of Disease Study. Lancet. 1997;349(9062):1347-52.
3. Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. Jama. 1999;282(7):677-86.
4. Organization WH. Global tuberculosis control: WHO report 2001. Global tuberculosis control: WHO report 2001: WHO; 2001.
5. Espinal MA, Laszlo A, Simonsen L, Boulahbal F, Kim SJ, Reniero A, et al. Global trends in resistance to antituberculosis drugs. New England Journal of Medicine. 2001;344(17):1294-303.
6. Pablos-Méndez A, Raviglione MC, Laszlo A, Binkin N, Rieder HL, Bustreo F, et al. Global surveillance for antituberculosis-drug resistance, 1994–1997. New England Journal of Medicine. 1998;338(23):1641-9.
7. Espinal MA, Kim SJ, Suarez PG, Kam KM, Khomenko AG, Migliori GB, et al. Standard short-course chemotherapy for drug-resistant tuberculosis: treatment outcomes in 6 countries. Jama. 2000;283(19):2537-45.
8. Lan N, Iademarco M, Binkin N, Tung L, Quy H, Cô N. A case series: initial outcome of persons with multidrug-resistant tuberculosis after treatment with the WHO standard retreatment regimen in Ho Chi Minh City, Vietnam. The International Journal of Tuberculosis and Lung Disease. 2001;5(6):575-8.
9. Park S, Kim C, Song S. Outcome of chemotherapy in 107 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. The International Journal of Tuberculosis and Lung Disease. 1998;2(11):877-84.
10. Tahaoğlu K, Törün T, Sevim T, Ataç G, Kir A, Karasulu L, et al. The treatment of multidrug-resistant tuberculosis in Turkey. New England Journal of Medicine. 2001;345(3):170-4.
11. Mitchison D. How drug resistance emerges as a result of poor compliance during short course

chemotherapy for tuberculosis [Counterpoint]. The International Journal of Tuberculosis and Lung Disease. 1998;2(1):10-5.
12. Ormerod L. Multidrug-resistant tuberculosis (MDR-TB): epidemiology, prevention and treatment. British medical bulletin. 2005;73(1):17-24.
13. Piatek AS, Telenti A, Murray MR, El-Hajj H, Jacobs WR, Kramer FR, et al. Genotypic analysis of Mycobacterium tuberculosis in two distinct populations using molecular beacons: implications for rapid susceptibility testing. Antimicrobial agents and chemotherapy. 2000;44(1):103-10.
14. Zhang Y, Heym B, Allen B, Young D, Cole S. The catalase—peroxidase gene and isoniazid resistance of Mycobacterium tuberculosis. 1992.
15. Telenti A, Imboden P, Marchesi F, Matter L, Schopfer K, Bodmer T, et al. Detection of rifampicin-resistance mutations in Mycobacterium tuberculosis. The Lancet. 1993;341(8846):647-51.
16. Drobniewski F, Pozniak A. Molecular diagnosis, detection of drug resistance and epidemiology of tuberculosis. British journal of hospital medicine. 1995;56(5):204-8.
17. Society JTCotBT. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. Thorax. 1998;53(7):536-48.
18. Ormerod L. Chemotherapy of tuberculosis. The European respiratory journal. 1997;12(Suppl 4):273-97.
19. Quy H, Lan N, Borgdorff M, Grosset J, Linh P, Tung L, et al. Drug resistance among failure and relapse cases of tuberculosis: is the standard re-treatment regimen adequate? The International Journal of Tuberculosis and Lung Disease. 2003;7(7):631-6.
20. Becerra M, Freeman J, Bayona J, Shin S, Kim J, Furin J, et al. Using treatment failure under effective directly observed short-course chemotherapy programs to identify patients with multidrug-resistant tuberculosis. The International Journal of Tuberculosis and Lung Disease. 2000;4(2):108-14.
21. García-García ML, Jiménez-Corona ME, Ponce-de-Leon A, Jimenez-Corona A, Palacios-Martinez M, Balandrano-Campos S, et al. Mycobacterium tuberculosis drug resistance in a suburban community in Southern Mexico [The Eddie O'Brien Lecture]. The International Journal of Tuberculosis and Lung Disease. 2000;4(12s2):S168-S70.