Multidrug-resistant-tuberculosis treatment in the Indian private sector: Results from a tertiary referral private hospital in Mumbai

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ABSTRACT

Background: There is very limited data on the experience and outcome of multidrug-resistant tuberculosis (MDR-TB) patients treated privately out of the DOTS plus program. Goal of this study is to provide characteristics and treatment outcomes of a prospective cohort of MDR-TB patients managed at a private tertiary referral institute. Materials and Methods: A prospective analysis of a cohort of MDR-TB patients treated in a tertiary private hospital, with the back-up of a Level 2 mycobacterial laboratory, which has recently received recognition by the Revised National Tuberculosis Control Program (RNTCP) for second-line drug susceptibility (DST). All patients received an individualized MDR regimen on an ambulatory basis. Results: Our 68% success rates are respectable and show that given the right laboratory backing, MDR-TB can be managed successfully in selected private practice settings.

KEY WORDS: India, individualized regimens, multidrug-resistant tuberculosis, private practitioners, private sector

INTRODUCTION

Tuberculosis (TB) is a major threat to world health. After HIV/AIDS, it is the most common cause of death from an infectious disease worldwide. A major obstacle to TB control is the emergence of mycobacterial resistance to anti-tuberculous chemotherapy. Multidrug-resistant tuberculosis (MDR-TB), is caused by strains of Mycobacterium tuberculosis that are resistant to Isoniazid and Rifampicin. The outcome results of MDR-TB patients remain suboptimal. In a recent meta-analysis, the cure rate for MDR-TB patients was reported at about 54% to 64%. Drug-resistant M. tuberculosis strains may account for 10% of the 8 million new cases of tuberculosis occurring annually worldwide. The latest WHO global resistance report, released in Oct. 2013, estimated that there were 79,000 cases of MDR-TB from India in 2012. This accounted for 17.6% of the world’s MDR-TB burden. Between them, India and China accounted for 50% of global MDR-TB.

There is a paucity of information on the management of Indian MDR-TB patients from the private sector. In this study we present data regarding the epidemiology, clinical characteristics, treatment strategies and outcome of a cohort of MDR-TB patients from a tertiary care private hospital in the city of Mumbai.

MATERIALS AND METHODS

The study was conducted in Mumbai in a tertiary referral center. Mumbai has a high MDR-TB burden.

This was a prospective observational descriptive study. We included consecutive patients having a microbiological diagnosis of MDR-TB presenting for consultation to a tertiary care private hospital in Mumbai from May 2006 to 2010. All patients had presented to a single chest consultant with a special interest in MDR-TB. Patients were only included for the study when cultures done at
On their first visit, sputum culture and drug-sensitivity testing (DST) to first- and second-line drugs were sent off to the microbiology laboratory of our hospital. This is a level 2 mycobacterial laboratory which has recently received WHO recognition as an Intermediate Reference Laboratory (IRL). TB culture is performed by the liquid culture i.e. Mycobacterial Growth Indicator Tube (MGIT) method with DST also being performed via the same methods. The critical concentrations used for the MGIT DST of the anti-TB drugs tested (13 in all) are as follows: Streptomycin 1 mcg/ml; Isoniazid 0.1 mcg/ml; Rifampicin 1 mcg/ml; Ethambutol 5 mcg/ml; Kanamycin 2 mcg/ml; Ethionamide 5 mcg/ml; PAS 4 mcg/ml; Ofloxacin 2 mcg/ml; Moxifloxacin 0.25 mcg/ml; Amikacin 1 mcg/ml; Clofazamine 0.5 mcg/ml; Capreomycin 2.5 mcg/ml and Pyrazinamide 100 mcg/ml.

The patients were analyzed on their initial visit with regard to their age, sex, occupation, income and prior treatment history. They were all initially prescribed an empirical drug regimen containing at least four drugs they had not previously received while awaiting their sensitivity report. The patients returned for their second consult with the DST (usually 6 to 10 weeks later) and were then prescribed a final individualized regimen based on this report and a knowledge of their past drug history. Patients were not on DOTS as these were private patients.

Whenever possible, an average of 5 new/sensitive drugs was chosen. On subsequent visits, at 2-3 monthly intervals, the patients weight, side effects due to drugs and changes made to the therapy were recorded. Sputum smears were done on every visit and sputum cultures at 3 monthly intervals. The radiological status was assessed with a chest X ray on each visit with a CT scan being performed if surgery was being contemplated. All the patients included in the study gave written informed consent and the hospital IRB gave approval for the study on 29 April 2006.

Data was collected at every patient visit from the hospital records by a research registrar.

For qualitative data Pearson’s Chi-square test was used to test the relationship of categorized dependent and independent variables. Normality of the data was checked by the Kolmogorov Smirnov test. The Mann Whitney U test was used to compare number of drugs with outcome. Statistics were all analyzed using SPSS 15.0 to analyze the data.

RESULTS

A total 78 patients with MDR TB were included. The mean age was 29.7 years ranging from 15 to 70 years. Forty-four (56.4%) were females and 34 (43.6%) were males. The patients were from areas in and around Mumbai but cases were referred from other states of India including Gujarat, Assam and Uttar Pradesh. Fever was the most common symptom occurring in 77 (98.7%) patients. Cough was seen in 71 (91%) patients. Hemoptysis was recorded in 18 (23.1%) patients. Radiologically, 33 (42.3%) patients had unilateral disease while 42 (53.8%) had bilateral and advanced disease. This was a heavily pre-treated population of TB patients. The average duration of anti-tuberculous treatment received by the group as a whole prior to referral to us was 20 months (range 2-120 months). Thirteen (16.6%) patients had received anti-tuberculosis drugs for 3 or more years. The average duration of second-line drug therapy in patients who had previously received these drugs was 22 months (range 3-96 months).

While, by definition, 100% of patients were resistant to isoniazid and rifampicin, sensitivity to pyrazinamide was retained in 67 (87%) of patients. Several patients were also resistant to multiple second-line drugs, with 50% of patients being fluoroquinolone resistant (pre-XDR). 7% of patients met the revised WHO diagnosis of XDR-TB. Overall, the cohort was resistant to a mean of 4.6 drugs. The resistance pattern has been summarized in Figures 1 and 2. A wide range of side effects was noted during therapy, some requiring discontinuation of the culprit drug as shown in Table 1.

Figure 1: Drug-specific resistance pattern

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Surgical resection of the infected lobe or lung was carried out in eight (10.2%) patients. Two underwent lobectomies and six underwent pneumonectomy. Of the 78 patients included in this study, 53 (68%) completed treatment and were declared cured while 12 (15%) failed treatment and 13 (16%) defaulted. The statistical analysis of those variables that are historically considered significant enough to alter outcome was made. These are shown in Table 2.

**DISCUSSION**

India has a large and expanding population of MDR-TB patients. A DOTS-plus strategy has just been introduced in a phased manner in India and the seven year pilot experience has been encouraging.[7] However, this still leaves uncovered the large numbers of MDR-TB patients who seek out private practitioners in an attempt to cure their MDR-TB. These private practitioners often are of varying standards, many of whom are inadequately qualified to deal with this problem. Their prescribing practice has received widespread censure and multiple treatment errors often served only to amplify drug resistance from MDR to XDR and beyond.[8] There are no clear national guidelines or microbiological lab facilities at their disposal. A careful literature search revealed almost no data on how Indian private practitioners manage their MDR-TB patients and what this study attempts to provide such data from a tertiary referral private hospital, with strong microbiology laboratory back up where a good sized cohort were treated on an ambulatory basis.

We observed a high prevalence in patients in a younger age group. The mean age of our MDR-TB cohort was 29.1 years. Females were more represented in our study. People from the lower socioeconomic strata were more likely to be affected by the disease but no stratum of society was exempt. Our patients had more severe and extensive disease, usually bilateral. We also observed that bilateral disease was the most significant marker of treatment failure in our group of patients (P value 0.092). A past history of tuberculosis was seen in almost 75% of our patients. This was expected as ours being a tertiary care centre most of the patients were referred. Our patients were a heavily pre-treated group of chronic MDR-TB patients. They had consulted an average of 2.6 doctors prior to visiting our center. In many ways they are representative of the majority of MDR-TB patients in this country who see multiple private practitioners with poor compliance rates. Physician-related treatment errors lead to development of MDR-TB.[9] Poorly prescribed second-line drugs only serve to amplify resistance and contribute to development of XDR-TB.

We feel access to a detailed DST from a reliable laboratory greatly contributed to our good outcomes. The use of individualized treatment, based on reliable DST is thus essential if these patents are to be successfully cured. Despite their poor resistance patterns we felt it was essential to offer each patient five to six new drugs in their regimen. Thus, Group 4 and newer drugs like linezolid were frequently resorted to in order to make up the required number of drugs essential for an effective regimen.

The recommended number of drugs used to treat MDR-TB is a subject of controversy. The ATS recommend four to six drugs for the treatment of MDR-TB.[10] The WHO however recommends at least four drugs.[11] The consensus is that more drugs may be required for more serious patients with previous use of second-line drugs or whose DST profile is adverse. Our patients were mainly referred, pre-treated patients and belonged to this category. The average number

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**Table 1: Frequency of drug usage and their side effects**

| Side effect                        | Drug                  | Frequency | Required discontinuation (numbers) |
|-----------------------------------|-----------------------|-----------|------------------------------------|
| Gastrointestinal (nausea, vomiting abdominal pain) | Isoniazid, Ethionamide | 32 (41%)  | 0                                  |
| Joint pains                        | Pyrazinamide, moxifloxacin | 12 (15.3%) | 2                                  |
| Peripheral neuropathy              | Linezolid             | 6/14      | 6                                  |
| Vestibular/ sensorineural deafness | Aminoglycosides       | 4/74      | 4                                  |
| Photosensitivity                   | Clofazamine, Sparfloxacin | 2         | 2                                  |
| Optic neuropathy                   | Linezolid             | 1         | 1                                  |
| Hypothyroidism                     | PAS, Ethionamide      | 1         | 0                                  |
| Visual field defects               | Ethambutol            | 1         | 1                                  |
| Hepatitis                          | Isoniazid, Rifampicin, Pyrazinamide | 3   | 3                                  |

PAS:Para-aminosalicylic acid

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**Table 2: Statistical analysis of the variables associated with adverse outcome in the study**

| Variables                        | P value | Relative risk |
|----------------------------------|---------|---------------|
| Unilateral vs. bilateral disease | 0.092   | 1.21          |
| 4 drugs vs. >4 drugs used        | 0.26    | 0.78          |
| Pyrazinamide                     | 0.442   | 1.14          |
| Linezolid                        | 0.449   | 0.87          |
| Previous second line drugs used  | 0.53    | 0.92          |
| XDR TB vs. MDR TB                | 0.60    | 1.15          |
| Surgery                          | 1.0     | 1.08          |
| Quinolones                       | 1.0     | 1.005         |

MDR-TB: Multidrug-resistant tuberculosis, XDR-TB: Extensively drug-resistant tuberculosis
of drugs used in our patients was 5.5. We believe including more drugs may have contributed to our success rates.\(^\text{[12]}\)

Our study found seven patients to have extensively drug-resistant tuberculosis (XDR-TB) defined as cases where TB isolates were resistant to isoniazid, rifampicin as well as to any quinolone and any injectable second-line drugs (Kanamycin, capreomycin, amikacin).\(^\text{[10]}\) Thus, about 10% of our MDR-TB patients have XDR-TB, which is in keeping with prior data on XDR-TB from the country.\(^\text{[13]}\)

The treatment principles applied to XDR-TB patients in our study were no different from MDR-TB and these patients had similar cure rates.

We observed high rates of resistance to streptomycin (75%) and fluoroquinolones (50%) in our patient population. Quinolones are broad-spectrum antibacterial agents which are the most widely prescribed group of antibiotics across India. Their widespread and indiscriminate use contributes to emergence of fluoroquinolone-resistant TB.\(^\text{[14]}\)

Fluoroquinolone resistance in MDR-TB is an emerging problem globally\(^\text{[15]}\) and has recently been reported from our center in India.\(^\text{[16]}\) The indiscriminate use of fluoroquinolones needs to be checked to control the spread of MDR-TB and XDR-TB.\(^\text{[17]}\)

Every attempt was made to incorporate a quinolone in our treatment regimen as quinolone use has been identified to be a good marker of successful outcome.\(^\text{[18]}\)

Among the quinolones, moxifloxacin was used the most frequently. The pharmacological profile of moxifloxacin with its relatively long half life and high area under the time-concentration curve suggests that this agent may be an ideal anti-TB drug.\(^\text{[19]}\) All our XDR-TB patients also received this drug despite (by definition) having ofloxacin resistance in their DST reports.

Susceptibility to PZA, PAS, Kanamycin and Ethionamide was retained in larger number of our TB isolates. Thus, if an empirical treatment regimen is planned (where culture and sensitivity is not available) these drugs should ideally be incorporated.

Linezolid has emerged as a useful drug for treatment of MDR TB with good in vitro susceptibility.\(^\text{[20]}\)

We used linezolid in 18 of our patients. The use of linezolid did not make any significant difference to the outcome. We observed severe side effects in seven of these patients requiring discontinuation of the drug. One case of bilateral optic neuropathy and six cases of severe peripheral neuropathy were seen.

The use of amino glycosides has also been recommended as injectable therapy is known to be a predictor of positive outcome. We attempted to continue the aminoglycoside for an average of 6 months in our patient cohort. Surgery was recommended in only 8 patients (10.5%) The majority of our patients had extensive bilateral disease at presentation. The cost of surgery was also a constraining factor in a private hospital. Some studies have shown the positive impact surgery can have in the management of MDR-TB.\(^\text{[21]}\)

Our MDR-TB cohort was treated exclusively on an out-patient basis. The cost of hospitalizing patients for MDR-TB as practiced in the West would be prohibitive. Several studies have shown that MDR-TB can be successfully treated on an outpatient basis.\(^\text{[22]}\)

The CDC, ATS and WHO all recommend a direct observational therapy for treatment of MDR-TB. Whilst DOTS has had a tremendous positive impact on tuberculosis in general, applying DOTS with its daily, complex regimens extending to periods of up to 24 months would not be practical in a resource poor country like India. Hence, while every effort was made to stress and ensure good compliance, and as much as a DOT approach would have been preferred, our private patients took self-supervised treatment. Wherever possible we recruited a responsible and motivated family member to help supervise the regular administration of the drugs advised.

There is meager data on the treatment outcome of MDR TB patients from India. Almost all available data is from the public sector. Ours is the first large-sized study from the private sector. Subhash et al.\(^\text{[23]}\) analyzed data in 100 patients retrospectively. They found a high default rate (45 patients) with 31 patients showing clinical and 13 showing radiological response. Another study from TRC Chennai\(^\text{[24]}\) showed that with an individualized treatment strategy in 66 patients' successful outcome was seen in 37% patients while 26% failed and 24% defaulted. A pilot study from the public sector has just been reported from New Delhi.\(^\text{[25]}\) This looked at DOTS-plus in an urban resource poor setting using DOTS-plus services under the existing RNTCP. This provided respectable cure rates of 61% in 126 MDR-TB patients.

A prospective study by Joseph et al. from Tamil Nadu (India) looked at the outcome of standardized treatment (RNTCP) for patients with MDR-TB, in 2007, included 38 MDR-confirmed patients and showed successful outcome in 66% (25/38).\(^\text{[26]}\)

A retrospective review of medical records of 11 adolescents enrolled between July 2007 and January 2013 was undertaken, in a Médecins Sans Frontières (MSF) project in Mumbai, India. Patients were initiated on either empirical or individualized second-line ambulatory anti-TB treatment under direct observation. Favorable results were seen in four (36.5%) patients: One was cured and three were still on treatment with negative culture results. Seven patients (64%) had poor outcomes: Four (36.5%) died and three (27%) defaulted.\(^\text{[26]}\)

Another retrospective study by Arora et al. analyzed the records of 66 patients with MDR-TB treated with a fully supervised standardized treatment regimen. Among 28 patients completing 2 years of treatment, 67.9% were cured, 14.3% died, 17.9% defaulted.\(^\text{[27]}\)
In a prospective study by Dhingra et al., 27 MDR-TB patients were included, from August 2002 to December 2004 at New Delhi Tuberculosis Centre and according to DST individualized treatment regimens were tailored. Of the 27 patients, 13 were cured and 10 defaulted. Radiological improvement was observed in two third of cases.[28]

In a cross-sectional study, conducted by Jana et al., in West Bengal, between January 2003 and January 2008, out of 1487 TB patients, 31 MDR-TB patients were identified and treated. Successful outcome was seen in 64.51%, relapse in 12.90%, treatment failure was seen in 19.35%.[29]

Despite the absence of DOT the number of patients who dropped out of our study was no more than had been reported in other studies. Our treatment success rate of almost 70% was equivalent to other Indian studies and is comparable to other international studies. We feel the two possible reasons behind our better success rates could be that all patients were under the care of a single physician with a special interest in MDR-TB and that our hospital mycobacterial laboratory has been reliably performing DST with good quality control over the last decade. Indeed it has recently been recognized as the sole Intermediate Reference Laboratory (IRL) for the city of Mumbai by WHO.

CONCLUSION

India houses one of the largest MDR-TB populations in the world. Till the government sponsored DOTS-plus programme expands, these unfortunate patients have very limited treatment options. Most Indian MDR-TB patients are compelled to visit private practitioners of varying standards in desperate attempts to cure their disease. This study shows that treatment of MDR-TB can be successful on an outpatient basis even in a resource-limited country like India. If managed outside the national programme, it should be undertaken in an experienced private centre with sound mycobacterial laboratory back-up. There is a paucity of data available on the treatment offered in the private sector to Indian MDR-TB patients. This study is an attempt to fill that gap. Our patient cohort was managed under optimal Indian conditions in a private hospital with an excellent laboratory backup. We hope these results inspire other Indian centers to take on the challenge of treating this disease and reporting their results in large numbers.

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