Research Article

Second-line drug resistance patterns among patients with multidrug-resistant tuberculosis of Gujarat, western India

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Abstract

Background: Lack of laboratory diagnostic capacity is a crucial barrier preventing an effective response to early and appropriate case detection and treatment of multidrug-resistant tuberculosis (MDR-TB). To date, limited representative drug resistance data are available from India on second-line drug (SLD) resistance.

Objectives: To study SLD resistance patterns in MDR-TB patients of Gujarat, western India.

Materials and Methods: Antituberculosis drug susceptibility testing of 50 MDR-TB isolates particularly for SLDs, namely p-aminosalicylic acid, ciprofloxacin, amikacin, D-cycloserine, kanamycin, and ethionamide, was conducted on solid Lowenstein–Jensen medium using the 1% proportion sensitivity method.

Results: Of 50 MDR-TB isolates tested, 24 (24/50, 48%) were found to be resistant to one or more SLDs. Of 50 MDR-TB isolates, 18 (18/50, 36%) showed resistance to ethionamide, 13 (13/50, 26%) to D-cycloserine, 11 (11/50, 22%) to ciprofloxacin, 7 (7/50, 14%) to kanamycin, 6 (6/50, 12%) to p-aminosalicylic acid, and 5 (5/50, 10%) to Amikacin.

Conclusion: High levels of SLD resistance were found to be present in this study. There is an urgent need for more control and rational use of the widely available fluoroquinolones and other SLDs outside of the Revised National Tuberculosis Control Programme, by both the public and the private health sectors in India.

KEY WORDS: Drug resistance, MDR-TB, second-line drugs

Introduction

One of the primary public health goals of the internationally recommended DOTS (directly observed treatment, short-course) strategy, the basic package that underpins the World Health Organization (WHO) Stop TB Strategy, is to prevent the development of multidrug-resistant tuberculosis [MDR-TB, defined as resistance to both isoniazid (INH) and rifampicin with or without resistance to other first-line drugs (FLDs)], which is difficult to cure and requires prolonged treatment with expensive and often toxic multidrug regimens.[1,2]

The overall proportion of MDR-TB was 5.3%, ranging from 0% to 35% of reported TB cases. On the basis of the survey data, the WHO estimates that, globally, nearly half a million new cases of MDR-TB occur each year.[3] The report also found that extensively drug-resistant TB (XDR-TB), that is, MDR-TB with resistance to fluoroquinolones (FQs) and one of the injectable second-line drugs (SLDs; capreomycin, kanamycin, and amikacin), which is more expensive and difficult to treat than MDR-TB, is widespread.[4]

Lack of laboratory diagnostic capacity is a crucial barrier preventing an effective response to early and appropriate case detection and treatment of MDR-TB. Today, less than 5% of the estimated numbers of MDR-TB patients are being detected, and just 2% are receiving the appropriate treatment.[5]

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To date, limited representative drug resistance data are available from India on SLD resistance. Thus, this work aimed to study SLD resistance pattern in MDR-TB patients of Gujarat, western India.

Materials and Methods

This study was carried out in tertiary care hospital, Ahmedabad, Gujarat, western India, from September 2010 to October 2011. Confirmed 50 MDR-TB isolates were collected from State Tuberculous Training and Demonstration Centre, Gujarat. Then, anti-TB drug susceptibility testing of MDR-TB isolates particularly for SLDs, namely *p*-aminosalicylic acid (0.5 µg/ml), ciprofloxacin (20 µg/ml), amikacin (20 µg/ml), D-cycloserine (30 µg/ml), kanamycin (20 µg/ml), and ethionamide (20 µg/ml), was carried out on solid Lowenstein–Jensen medium using the 1% proportion sensitivity method as per the WHO guidelines.[6] All isolates came from patients with a history of one or more previous courses of treatment, with many having chronic smear-positive pulmonary TB. The exact clinical history and the human immunodeficiency virus status of patients were, however, not available for this retrospective evaluation.

Results

In this study, total 50 confirmed MDR-TB isolates were tested for anti-TB susceptibility pattern for SLDs. Of 50 MDR-TB isolates tested, 24 (24/50, 48%) were found to be resistant to one or more SLDs. Thus, 26 (26/50, 52%) isolates were susceptible to one or more SLDs.

Of 50 MDR-TB isolates, 18 (18/50, 36%) showed resistance to ethionamide (ET), 13 (13/50, 26%) to D-cycloserine (DC), 11 (11/50, 22%) to ciprofloxacin (CP), 7 (7/50, 14%) to kanamycin (KA), 6 (6/50, 12%) to p-aminosalicylic acid (PA), and 5 (5/50, 10%) to amikacin (AM).

Among 50 MDR-TB isolates, only 1 (1/50, 2%) isolate showed resistance to CP, ET, and PA. According to the number of drugs to which patient is resistant to SLDs, maximum resistance is seen in isolates having two drugs resistance [Table 1].

Discussion

Control of TB remains one of the most challenging issues in global health. A new and potentially devastating threat to TB control is the emergence of strains that cannot be cured by standard anti-TB drug regimens. Drug resistance rates are regarded as one of the most important aspects of surveillance in the National TB Control Program in India.[7]

Table 1: No. of drugs to which patient is resistant to SLDs

No. of drugs	*n*	%
1	3	6
2	12	24
3	6	12
4	1	2
5	1	2
6	1	2

As the study group was a highly selective one, comprising mainly treatment failures and chronic cases. High levels of MDR-TB among previously treated patients can be due to poorly designed drug regimens, poor patient adherence to treatment, and poor drug quality. However, in India, all anti-TB drugs, both FLDs and SLDs, are widely available and used, often irrationally, in the private and the public sectors outside of the Revised National Tuberculosis Control Programme (RNTCP).[8]

In this study, the rate of resistance among MDR-TB isolates to one or more SLDs was 48% (24/50), which is comparable with the rate of resistance reported by Paramasivan et al.[9] (52%), and by Ramachandran et al.[10] (56%).

Rate of resistance to ET in this study was 36% (18/50). Similarly, the rate of ET resistance was reported to be 33% by Paramasivan et al.[9] and 28% by Ramachandran et al.[10] The rate of resistance to ET is difficult to interpret because technical issues with the DST make the results of limited reliability. Hence, not all observed ET resistance can be attributed to use of this drug in clinical settings and to the role of cross-resistance with INH due to mutations in the *inh*A gene and others. A subset of such ET-resistant isolates tested for the *inh*A gene showed a 40% prevalence of this mutation, which may account for the high *in vitro* resistance to ET that was observed.[11–13]

Among MDR-TB isolates, we detected an unprecedented prevalence of any resistance to CP to be 22% (11/50). Similarly, an unprecedented prevalence of any resistance to CP was reported to be 16.4% by Paramasivan et al.[9] and 24% by Ramachandran et al.[10] The high level of resistance to FQs (i.e., CP in this instance) correlates well with the widespread use of FQs for the treatment of new TB cases in the private sector and its irrational use for pyrexia of unknown origin and respiratory infections that could be undiagnosed TB in India. This is in line with other reports from elsewhere in the world where high rates of resistance to FQs are reported. Case reports have shown that even a short duration of monotherapy with FQs can quickly result in acquired resistance in Mycobacterium tuberculosis. Regardless of the reason, resistance to FQs has serious implications. First, FQs are crucial for the treatment of MDR-TB, and resistance to FQs has been independently associated with poor MDR-TB treatment outcomes. Patients with resistance to FQs are also at risk of developing XDR-TB during treatment with SLDs, a risk that may increase if these drugs are administered outside the setting of a structured and supportive treatment program.[14–18]

Among MDR-TB isolates, 14% (7/50) showed resistance to KA and 10% (5/50) to AM. Paramasivan et al.[9] reported that 11.3% isolates were resistant to KA. The low levels of KM resistance seen in Gujarat could be due to the very limited use of this drug in the private sector, and also because of the ease of prescribing FQs.

Resistance to PA was found in 12% (6/50) of isolates. About 16% resistance to PA was also reported by Lai et al.[19]

In our study resistance to DC was found to be in 26% (13/50) isolates. This was in line with the finding of Dam et al.[20], who showed the resistance of 23.5%. This resistance may be partially attributed to cross-resistance among drugs (e.g., cross-resistance of ET with INH).

Conclusion

In conclusion, although there was a decreasing overall trend of anti-TB drug resistance in recent years, the prevalence of MDR-TB remains high, and the presence of resistance to SLDs will impose a new challenge in the control of TB. Continuous surveillance of clinical isolates of *M. tuberculosis* is needed to identify MDR-TB or XDR-TB, especially in patients with a history of TB and those who have received prior anti-TB treatment.

As the RNTCP expands its diagnostic and treatment services for MDR-TB cases, there will be a potential threat to the standardized Category IV treatment regimen if such high levels of SLDs resistance are present in enrolled patients. There is, therefore, an urgent need for more control and rational use of the widely available FQs and other SLDs outside of the RNTCP, by both the public and the private health sectors in India. In general, new SLD regimens and better rapid diagnostic tests are needed for effective detection and treatment of MDR-TB.

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