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# Linezolid: an effective, safe and cheap drug for patients failing multidrug-resistant tuberculosis treatment in India

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**ABSTRACT: Linezolid is identified as an effective drug with which to treat patients failing multidrug-resistant (MDR)-tuberculosis (TB) treatment. However, cost and safety are the concerns. In India, the average price of a 600-mg pill of linezolid is less than one US dollar, much cheaper than most of the third-line drugs.**

**A prospective study of 29 MDR-TB treatment failure patients (16 with laboratory-proven extensively drug-resistant (XDR)-TB and the remaining 13 with MDR-TB with resistance to any quinolone but sensitive to injectables) was carried out in Delhi, India. All patients received daily unsupervised therapy with linezolid, one injectable agent, one fluoroquinolone and two or more other drugs.**

**Patients received a median of six anti-mycobacterial agents. Besides linezolid, capreomycin, moxifloxacin, levofloxacin and amoxycillin-clavulanic acid were used in 41.4%, 58.6%, 41.4%, and 79.3% of patients. Out of a total of 29 patients, 89.7% patients achieved sputum smear and culture conversion; 72.4% showed interim favourable outcome; 10.3% died, 6.8% failed and 10.3% patients defaulted. Linezolid had to be stopped in three (10.3%) patients due to adverse reactions. The outcome of treatment of 16 XDR-TB patients was comparable to the other 13 MDR-TB patients.**

**Linezolid is an effective, cheap and relatively safe drug for patients failing MDR-TB treatment, including those with confirmed XDR-TB.**

**KEYWORDS: Extensively drug-resistant, linezolid, multidrug-resistant tuberculosis**

Extensively drug-resistant (XDR)-tuberculosis (TB) is defined as a disease caused by *Mycobacterium tuberculosis* isolates resistant to at least isoniazid and rifampicin (multidrug resistant (MDR)-TB) and, additionally, to any fluoroquinolone and one second-line injectable drug [1]. The prognosis of XDR-TB patients [2–4] is worse than that of MDR-TB patients [3, 5, 6]. In XDR-TB patients, a favourable outcome can vary from 20% to 60% depending upon factors such as fluoroquinolone resistance, previous TB treatment, directly observed therapy throughout, MDR-TB treatment duration and surgical resection [2–4]. The key drugs in the management of MDR-TB and XDR-TB patients are newer fluoroquinolones [6–8] and second-line injectables [9, 10].

Several studies have shown that linezolid is an effective third-line drug for the management of the MDR- and XDR-TB patients [11, 12]. Linezolid use in the regimen has been found to improve the favourable outcome among XDR-TB patients [4]. Its use has been limited because of its high price in many countries and its relatively higher toxicity profile [11–14]. However, in India, the average market price of a 600-mg pill of linezolid is less than one US dollar, which is much cheaper than most second- and third-line drugs.

We have previously reported our experience with MDR-TB patients from India under field conditions [15]. However, due to the lack of quality-assured laboratories to carry out drug susceptibility testing (DST) against second-line drugs [16], the burden of XDR-TB and its treatment outcomes in India are not yet adequately known. The aim of this study was to describe the bacteriological and radiological profile and treatment outcome using linezolid with various other second- and newer third-line anti-tuberculosis drugs among patients who have failed to a previous MDR-TB treatment. This would contribute to the growing knowledge on XDR-TB management in India and to the role of linezolid in the treatment of these patients.

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## METHODS

We report herein a prospective case series at a tertiary level institute in Delhi, India, using linezolid in patients failing MDR-TB treatment. These patients had laboratory-proven XDR- or MDR-TB with resistance to any quinolone without second-line injectable drug resistance (classified as pre-XDR-TB). Patients were enrolled from January 2006 onwards and were given individualised tuberculosis treatment. The interim results were analysed in January 2011 among patients who had completed >1 yr of treatment. The cost of treatment was borne either by the patients themselves or through their local funding agencies. The study was approved by the institutional ethical board of the institute. Written informed consent was obtained from all patients.

Sputum smear, culture and DST for first- and second-line drugs of all patients were tested at the National Reference Laboratory (NRL) situated in the same institute. The laboratory is validated by the Supranational Reference Laboratory (Tuberculosis Research Centre, Chennai, India). DST was performed using the absolute concentration method on Lowenstein–Jensen medium [16]. Besides first-line drugs, DST was performed for ofloxacin, kanamycin, amikacin, capreomycin, ethionamide, para-aminosalicylic acid (PAS) and cycloserine. All patients were given an individualised treatment regimen determined on the basis of prior treatment history and DST results, irrespective of the radiological pattern, severity of disease and prior hospitalisation.

The regimens were constructed with a goal of prescribing at least five anti-tuberculosis agents that were likely to be effective. All patients received daily therapy with linezolid, one injectable agent, one fluoroquinolone and two or more second- or third-line drugs (table 1). The dosages of the drugs used are summarised in table 1. Major adverse reactions were defined as reactions requiring permanent discontinuation of the suspected offending drug. During treatment, drugs could be substituted if any major adverse drug reaction occurred.

The intensive phase (IP) consisted either of an injectable drug with other oral drugs for at least 6 months or culture conversion, whichever was later. The continuation phase consisted of oral agents for at least 18 months after IP. Surgery was considered in patients not showing adequate response to anti-tuberculosis medication and having localised disease.

All patients were hospitalised initially for pre-treatment evaluation and to watch for early adverse effects. Sputum smear and culture for acid-fast bacillus (AFB) was performed monthly in IP and once every 2 months afterwards until treatment completion. After discharge, the patients were seen as outpatients once every 2 weeks. The compliance to treatment was ensured by checking the empty blister packs on the subsequent visit. All patients were managed by the same team of doctors throughout the course of treatment.

International definitions of treatment outcomes were used for the analysis [17]. Treatment outcomes included cured, treatment completion, still on treatment, failure, died and defaulted. Culture conversion was defined as two consecutive negative cultures collected at least 30 days apart. Patients who

**TABLE 1** Drugs used in the 29 patients taking part in the study

| | Subjects | Dosages for patient weight mg | |
|---|---|---|---|
| | | <45 kg | ⩾45 kg |
| **Single drug use group** | | | |
| Kanamycin | 15 (51.7) | 500 *q.d.* | 750 *q.d.* |
| Capreomycin | 12 (41.4) | 500 *q.d.* | 750 *q.d.* |
| Amikacin | 2 (6.8) | 500 *q.d.* | 750 *q.d.* |
| Levofloxacin | 12 (41.4) | 750 *q.d.* | 750 *q.d.* |
| Moxifloxacin | 17 (58.6) | 400 *q.d.* | 400 *q.d.* |
| Ethionamide | 14 (48.3) | 250 *b.i.d.* | 750 in divided doses |
| Clofazimine | 12 (41.4) | 200 *q.d.* | 200 *q.d.* |
| Prothionamide | 11(37.9) | 250 *b.i.d.* | 750 in divided doses |
| PAS | 19 (65.5) | 10000 in divided doses | 12000 in divided doses |
| Cycloserine | 10 (34.4) | 250 *b.i.d.* | 750 in divided doses |
| Amoxycillin-clavulanic acid | 23 (79.3) | 625 *t.i.d.*/1000 *b.i.d.* | 625 *t.i.d.*/1000 *b.i.d.* |
| Linezolid[#] | 29 (100) | | |
| High dose | 11(37.9) | 600 *b.i.d.* | 600 *b.i.d.* |
| Low dose | 18 (62.1) | 600 *q.d.* | 600 *q.d.* |
| **Drug combination group[¶]** | | | |
| L+I+Q+2 drugs | 3 (10.3) | | |
| L+I+Q+3 drugs | 16 (55.2) | | |
| L+I+Q+4 drugs | 6 (20.7) | | |
| L+I+Q+5 drugs | 4 (13.8) | | |

Data are presented as n (%), unless otherwise stated. PAS: para-aminosalicylic acid; L: linezolid; I: injectable; Q: quinolone. [#]: linezolid was given either as low dose (600 mg *q.d.*) or high dose (600 mg *b.i.d.*); [¶]: median (interquartile range) number of drugs used was 6 (6–7).

completed treatment will continue to be screened clinically and bacteriologically for the next 2 yrs for recurrent disease either once every 3 months or on a need basis.

### *Statistical analysis*

The data were analysed using Microsoft Excel 2007 (Microsoft Corp., Redmond, WA, USA) and SPSS software version 12.0 (SPSS, Inc., Chicago, IL, USA). Comparisons of outcomes between XDR- and pre-XDR-TB patients, and between the different strata, such as anthropometric characteristics, sputum conversions, radiological features and treatment outcomes, were performed using Pearson's Chi-squared tests. p-values $<0.05$ were considered to be significant. Yates' correction and Fisher's exact test were applied wherever indicated. For parametric data, the unpaired t-test was used. For nonparametric data, the Mann–Whitney U-test was used.

## RESULTS

A total of 29 patients who completed >12 months of treatment from January 2006 until January 2011 were evaluated in the current study. The median cumulative duration of hospital care was 30 days (range 5–54 days), with an interquartile range of 21–44 days. The demographic profile of these patients is shown in table 2. 16 (55.2%) patients had XDR-TB and 13 (44.8%) had pre-XDR-TB. The median age was 29 yrs (range 15–46 yrs). All patients were HIV negative. Four (13.8%) patients had history of controlled diabetes, but none of them had any other chronic illness. 17 (58.6%) patients had anaemia (defined in the study as haemoglobin $<10$ g·dL$^{-1}$). XDR-TB patients had taken three or more previous treatments more often than those with pre-XDR-TB. However, the difference was not statistically significant (p=0.588). 12 (41.4%) patients had history of contact with TB patients at home but none had history of contact with MDR- or XDR-TB at home.

The radiological investigation showed that 19 (65.5%) patients had cavitation while, in 20 (69%), the disease was bilateral. In 12 (41.4%) and 17 (58.6%) patients, lesion was far advanced and moderately advanced, respectively (table 3) [18]. There was no statistically significant difference between XDR-TB and pre-XDR-TB groups of patients regarding their radiological profile. The bacteriological profile of the patients is shown in table 3.

Patients received a median of six anti-mycobacterial agents (interquartile range 6–7 drugs). Under study, three (10.3%), 16 (55.2%), six (20.7%) and five (17.2%) patients received five, six, seven and more than seven drugs for treatment respectively (table 1). Linezolid was used in all the patients while capreomycin, moxifloxacin, levofloxacin and amoxycillin-clavulanic acid were used in five (17.2%), 17 (58.6%), 12 (41.4%) and 23 (79.3%) patients.

26 (89.7%) patients achieved sputum smear and culture conversion (tables 4 and 5) by the end of 6 months. Three patients remained persistently culture positive; treatment was stopped after 15 months of treatment in two patients, while one patient died at 8 months of treatment. As with the intention-to-treat analysis, the median time for sputum AFB smear and culture conversion was 4 months (interquartile range 3–5 months). 21 (80%) patients achieved smear conversion and 18 (69%) culture conversion by the end of 4 months of treatment. There was no statistically significant difference between XDR-TB and pre-XDR-TB patients in the median time for smear and culture conversion.

**TABLE 2** Demographic and other characteristics of 29 patients taking part in the study

| | XDR-TB | Pre-XDR-TB | p-value | Total |
|---|---|---|---|---|
| **Subjects n** | 16 | 13 | | 29 |
| **Age yrs** | | | | |
| Median | 28 | 36 | | 29 |
| Range | 15–46 | 18–46 | | 15–46 |
| Interquartile range | 18–39 | 27–40 | | 21–40 |
| **Sex M:F** | 1:3 | 1.6:1 | | |
| **Geographical** | | | | |
| Urban | 9 (56.2) | 8 (61.5) | 0.774 | 17 (58.6) |
| Rural | 7 (43.7) | 5 (38.5) | | 12 (41.4) |
| **Previous treatment** | | | | |
| Median duration months | 14 | 13 | | 16 |
| Range months | 6–22 | 6–21 | | 6–22 |
| Interquartile range months | 12–16 | 12–16 | | 12–16 |
| Number of previous treatments | | | | |
| One | 2 (12.5) | 3 (23.1) | 0.798# | 5 (17.2) |
| Two | 5 (31.3) | 4 (30.8) | 0.707# | 9 (31.0) |
| Three or more | 9 (56.2) | 6 (46.1) | 0.588 | 15 (51.8) |
| **Smokers** | 2 (12.5) | 6 (46.1) | 0.110# | 8 (27.6) |
| **Family history** | | | | |
| TB | 5 (31.2) | 7 (53.8) | 0.219 | 12 (41.4) |
| MDR/XDR-TB | 0 | 0 | | 0 |
| **Anaemia** | 12 (75) | 5 (38.5) | 0.047 | 17 (58.6) |
| **Diabetes** | 2 (12.5) | 2 (15.4) | 0.75# | 4 (13.8) |
| **HIV** | 0 | 0 | | 0 |
| **Radiology** | | | | |
| Presence of cavity | 11 (68.7) | 8 (61.5) | 0.989# | 19 (65.5) |
| Bilateral | 11 (68.7) | 9 (69.2) | 0.707# | 20 (69.0) |
| Extent of lesion | | | | |
| Mild | 0 | 0 | | 0 |
| Moderately advanced | 8 (50) | 9 (69.2) | 0.296 | 17 (58.6) |
| Far advanced | 8 (50) | 4 (30.8) | 0.296 | 12 (41.4) |

Data are presented as n (%), unless otherwise stated. XDR-TB: extensively drug-resistant tuberculosis; pre-XDR-TB: multidrug-resistant (MDR)-TB plus quinolone resistance without resistance against injectables; M: male; F: female. #: Yates' correction applied.

Major adverse events requiring permanent discontinuation of the offending drug were observed in five (17.2%) patients. These included severe anaemia, peripheral neuritis and optic neuritis due to linezolid in one patient each, hearing loss due to capreomycin in one patient and major psychosis due to cycloserine in one patient. In only three (10.3%) patients receiving linezolid was it necessary to stop this drug permanently; all three were receiving high-dose linezolid (600 mg *b.i.d.*). Minor adverse reactions, such as loss of appetite (39%), mild anaemia (32%), nausea and vomiting (17.8%), and mild peripheral neuritis (13.8%), could be managed by ancillary drugs or temporary discontinuation of offending drugs.

**TABLE 3** Bacteriological profile of 29 patients taking part in the study[#]

| | |
|---|---|
| **XDR** | 16 (55.2) |
| **Pre-XDR-TB** | 13 (44.8) |
| **MDR+any one SLD** | 10 (34.5) |
| **MDR+any two SLDs** | 3 (10.3) |
| **MDR+any three SLDs** | 12 (41.4) |
| **MDR+any four SLDs** | 4 (13.8) |
| **Any drug resistance** | |
| Kanamycin | 12 (41.4) |
| Capreomycin | 5 (17.2) |
| Amikacin | 7 (24.1) |
| Ofloxacin | 29 (100) |
| Ethionamide | 13 (44.8) |
| Clofazimine | 11 (37.9) |
| Prothionamide | 7 (24.1) |
| PAS | 8 (27.6) |
| Cycloserine | 8 (27.6) |

Data are presented as n (%). XDR: extremely drug resistant; TB: tuberculosis; pre-XDR-TB: multidrug-resistant (MDR)-TB plus quinolone resistance without resistance against injectables; SLD: second-line drug resistance; PAS: para-aminosalicylic acid. [#]: drug-susceptibility testing against amoxycillin-clavulanic acid, linezolid, levofloxacin and moxifloxacin was not performed.

Table 6 shows treatment outcomes among 29 patients enrolled in the study. Nine (31%) patients were cured. Another 12 (41.4%) patients completed >12 months of treatment and are persistently culture negative. Therefore, a total of 21 (72.4%) patients showed interim favourable outcome. Among 11 patients on high-dose linezolid therapy (600 mg *b.i.d.*), eight (72.7%) achieved interim favourable outcome, while among 18 patients on low-dose linezolid (600 mg *q.d.*) therapy, 13 (72.2%) achieved interim favourable outcome. The difference was not statistically significant (p=1.0).

Three (10.3%) patients died at 8, 10 and 12 months of treatment; all due to respiratory failure. Two of them were persistently smear and culture negative at the time of death. Three (10.3%) patients defaulted; two due to inability to afford the high cost of treatment at 10 and 14 months each and one due to migration at 16 months. These three were also persistently smear and culture negative at the time of default. Two (6.8%) patients were declared failed, as the treatment had to be stopped at 15 months due to persistent sputum positivity accompanied by no clinical response. There was no statistically significant difference in outcomes between pre-XDR-TB and XDR-TB patients (table 6). After being cured, nine patients are at the time of publication under follow-up with an average period of 12.8 months (range 6–28 months). None has relapsed so far. Surgery was performed in two patients with XDR-TB. Both patients had favourable outcomes.

## DISCUSSION

The treatment of XDR-TB presents a major challenge. Former treatment mismanagement may substantially contribute to the development of drug resistance [19–21]. This study shows that an aggressive and comprehensive management programme using linezolid can favourably treat more than 70% of patients with XDR-TB or pre-XDR-TB who have previously received numerous unsuccessful anti-tuberculosis treatments with first- and second-line drugs.

It is noteworthy that the outcomes in the present study were better than those previously reported in our MDR-TB patients, where of the 126 patients enrolled, 61% were cured, 19% died, 18% defaulted and 3% failed treatment [15]. Our outcomes were even better than the studies showing the best outcomes in the recently published meta-analysis of XDR-TB treatment outcomes by JACOBSON *et al*. [2]. The only factor associated with a better outcome in this meta-analysis was the use of a later generation of fluoroquinolone. The six studies where at least 50% of the XDR-TB patients received a later generation of fluoroquinolones showed a median favourable outcome of 59% [2], clearly less than 72% of the interim favourable outcomes of our study. The best outcomes published to date regarding XDR-TB patients have been achieved by KWON *et al*. [22] in Korea (67% in 27 patients) and by MITNICK *et al*. [23] in Peru (60% in 48 patients); both are inferior to our study results. In contrast to the study in Peru [23], our patients did not have good nutritional and psychosocial support. Also, the treatment was not fully supervised. However, the compliance to treatment was ensured by checking the empty blister packs on the subsequent visit. All the patients were routinely managed by the same team of doctors on a domiciliary basis. This could explain the low default rate observed in our study.

In the current study, the unfavourable outcome of treatment of pre-XDR-TB was comparable to the XDR-TB group. This again raises concern about the impact of fluoroquinolone resistance on poor treatment outcome. KIM *et al*. [10], in South Korea,

**TABLE 4** Smear conversion characteristics in 29 patients

| | XDR | Pre-XDR-TB | Total | p-value |
|---|---|---|---|---|
| **Subjects** | 16 | 13 | 29 | |
| **Smear conversion** | 15 (93.7) | 11 (84.6) | 26 (89.7) | 0.87 |
| **Median time for smear conversion months** | 4 | 4 | 4 | 0.55 |
| **Culture conversion** | 15 (93.7) | 11 (84.6) | 26 (89.7) | 0.87 |
| **Median time for culture conversion months** | 4 | 4 | 4 | 1.00 |

Data are presented as n or n (%), unless otherwise stated. XDR: extremely drug resistant; TB: tuberculosis; pre-XDR-TB: multidrug resistant-TB plus quinolone resistance without resistance against injectables.

**TABLE 5** Cumulative conversion characteristics in 26 patients

| | Smear conversion | Culture conversion |
|---|---|---|
| **Up to 1 month** | 0 | 0 |
| **Up to 2 months** | 4 (15.4) | 3 (11.5) |
| **Up to 3 months** | 11 (42.3) | 9 (34.2) |
| **Up to 4 months** | 21 (80.8) | 18 (69.2) |
| **Up to 5 months** | 26 (100) | 24 (92.3) |
| **Up to 6 months** | 26 (100) | 26 (100) |

Data are presented as n or n (%).

also reported that patients with either form of pre-XDR-TB (resistance to ofloxacin or second-line injectable drugs) showed poorer cumulative survival than those with ofloxacin-susceptible/injectable-susceptible MDR-TB. Thus, it seems very clear that fluoroquinolones are the key in the outcome of MDR-TB and even XDR-TB treatment. Regarding the role of the second-line injectable drugs in the favourable outcome of the MDR-TB patients, the situation is little controversial [6, 9, 24], although some recent studies suggest that their role is key [25, 26].

This study also reflects the importance of using later-generation fluoroquinolones in the treatment of MDR- and XDR-TB. Moxifloxacin and levofloxacin were commonly included in the individualised regimens, even in patients with isolates that were resistant to ofloxacin. This practice is supported by evidence that the efficacy of later-generation fluoroquinolones may be preserved, despite resistance to ofloxacin or ciprofloxacin [2].

The role of linezolid in the treatment of MDR-TB and XDR-TB has been considered controversial. In spite of the excellent pharmacological properties against *M. tuberculosis* discovered >10 yrs ago [27] and the good results communicated in some studies [12, 28, 29], the findings of the recent multinational study of MIGLIORI *et al*. [11], addressing the assessment of linezolid safety, tolerability and efficacy in MDR-TB patients, were a little disappointing. The conclusions of the study by MIGLIORI *et al*.

**TABLE 6** Treatment outcomes in 29 patients

| | XDR | Pre-XDR-TB | p-value | Total |
|---|---|---|---|---|
| **Cured** | 5 (31.2) | 4 (30.8) | 0.707# | 9 (31.0) |
| **Still on treatment¶** | 7 (43.7) | 5 (38.5) | 0.774 | 12 (41.4) |
| **Failed** | 0 | 2 (15.4) | 0.192+ | 2 (6.8) |
| **Default** | 2 (12.5) | 1 (7.7) | 0.849# | 3 (10.3) |
| **Died** | 2 (12.5) | 1 (7.7) | 0.849# | 3 (10.3) |
| **Total** | 16 (100) | 13 (100) | | 29 (100) |

Data are presented as n (%), unless otherwise stated. XDR: extremely drug resistant; TB: tuberculosis; pre-XDR-TB: multidrug resistant-TB plus quinolone resistance without resistance against injectables. #: Yates' correction applied; ¶: all patients completed >12 months of treatment and, to date, are persistently culture negative; +: Fisher's exact test applied.

[11] were that linezolid (600 mg *q.d.*) added to an individualised multidrug regimen may improve the chance of bacteriological conversion, providing a better chance of treatment success in only the most complicated MDR/XDR-TB cases. However, its safety profile did not warrant use in cases for which other safer alternative drugs were available. Also twice-daily administration produced more major side-effects than once-daily dosing, with no difference in efficacy [11].

However, in the present study, linezolid had to be stopped in only three (10.3%) patients because of serious adverse effects; all three were using 600 mg *b.i.d.*. Also the efficacy of low-dose linezolid was comparable to high-dose therapy. Our results regarding the efficacy and good tolerance of linezolid is very different to other experiences in India, where the use of linezolid was not associated with any difference in treatment outcome and where 61% of the patients had major adverse reactions [13]. On the contrary, CONDOS *et al.* [29] achieved favourable outcomes in 50% of their XDR-TB patients by using linezolid systematically in all their patients. It is also possible that linezolid may had contributed to the good outcomes (57% favourable outcome) achieved by EKER *et al.* [30] in Germany using linezolid in 71.4% of their XDR-TB patients.

The two most important limitations to using linezolid systematically in all the XDR-TB or pre-XDR-TB patients are the high price and the rate of serious adverse events. It is very important to highlight that price is not a limiting factor in India, where the price of a 600-mg pill is less than one US dollar (much cheaper than most second-line drugs). Also, it seems that the rate of adverse events can clearly be reduced (without any decrease in the efficacy) by using only 600 mg *q.d.* [11, 14]. There are some promising studies showing that 300 mg *q.d.* could further reduce the rate of adverse events [31]. It is necessary to ensure that this low dose does not reduce the efficacy of this drug.

In the present study, linezolid was used in all 29 patients, and amoxycillin-clavulanic acid, clofazimine and moxifloxacin were used in 79.3%, 41.4% and 58.6% patients respectively. Although evidence of the efficacy of these drugs, other than moxifloxacin, is limited at best, we cannot exclude the possibility that one or more of these drugs contributed to treatment success, either by increasing the regimen's activity or by providing protection against the emergence of resistance to other more active agents.

Out of 29 patients, 26 (89.7%) achieved sputum smear and culture conversion by the end of 6 months. Mean time for smear conversion was 3.1 months and for culture conversion was 3.9 months, and the median time for smear as well as culture conversion was 4 months. The time taken for smear or culture conversion was comparable to other studies. In the systematic review by SOTGIU *et al.* [3] among XDR-TB patients, the median time for smear conversion ranged from 88 to 110 days and for culture conversion from 60 to 195 days. Also, our current sputum conversion is even better that previously published for our MDR-TB patients, where out of 126 MDR-TB patients, 100 (79%) patients achieved sputum culture conversion within 8 months [15].

In our study, two (6.8%) patients failed treatment because the treatment had to be stopped due to persistent sputum

positivity and deterioration in clinical condition. Failure rate in XDR-TB has ranged from 10.4% to 31% in previous studies [3], and the death rate was 10.3%. The death rate in XDR-TB ranged from 7% to 36% in previous studies [3]. Low death rate and low failure rate could be due to the efficacy of drugs used in the study. In our present study, serious adverse events requiring discontinuation of the offending drug were observed in only five (17.2%) patients. Review of previous studies also suggests that adverse drug reactions are not a major limiting factor for the management of XDR-TB patients [3].

In our study, two (6.8%) XDR-TB patients were referred for resectional surgery; both did well after surgery and were finally cured. Surgical resection may be a potentially useful strategy for a condition that cannot be adequately controlled with drug-based intervention [3, 4, 32].

A significant number of patients being studied have still not completed the treatment. This and the small number of patients are limitations of our study. Additionally, a long follow-up period of cured patients is required before we can comment on lasting cures among treated patients. However, the good interim outcomes are still valid, regardless of these limitations.

To conclude, this study shows that an aggressive, comprehensive management programme using linezolid along with other drugs can favourably treat significant number of patients with XDR-TB or pre-XDR-TB. Linezolid could have played a key role in treatment of these patients. Linezolid was also observed to be a cheap (in India) and relatively safe drug to use. The misuse of quinolones should be avoided, as MDR-TB with quinolone resistance without XDR-TB can be associated with poor outcomes compared with XDR-TB patients. More experience and long-term follow-up are also needed for newer third-line drugs.

## STATEMENT OF INTEREST

None declared.

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