Case Report

Early experience of delamanid in extensively drug-resistant pulmonary tuberculosis

Vikas Marwah[1], Prashant R. Patil[2], Robin Choudhary[1], Virender Malik[3]

[1]Department of Pulmonary, Critical Care and Sleep Medicine, Army Institute of Cardiothoracic Sciences, Pune, Maharashtra, India, [2]Department of Pathology, Army Institute of Cardiothoracic Sciences, Pune, Maharashtra, India, [3]Department of Radiology, Army Institute of Cardiothoracic Sciences, Pune, Maharashtra, India

ABSTRACT

Tuberculosis is a leading cause of death in our country. Multidrug-resistant tuberculosis increases the morbidity and mortality due to severe manifestations and difficult and prolonged medications. Newer antitubercular drugs like delamanid have been approved by WHO in management of these cases, but the real-world experience of this drug is lacking in our country. We present our early experience of use of delamanid in extensively drug-resistant pulmonary tuberculosis.

KEY WORDS: Delamanid, extensively drug-resistant tuberculosis, sputum smear positive pulmonary tuberculosis

Address for correspondence: Dr. Robin Choudhary, Department of Pulmonary, Critical Care and Sleep Medicine, Army Institute of Cardiothoracic Sciences, Pune, Maharashtra, India.
E-mail: robinch19@gmail.com

Submitted: 12-Sep-2022 **Revised:** 16-Oct-2022 **Accepted:** 19-Oct-2022 **Published:** 29-Dec-2022

INTRODUCTION

Drug-resistant tuberculosis is an emerging threat to the healthcare system. According to the latest World Health Organization statistics, about 4% of new TB patients and 19% of previously treated patients can be having resistance to rifampicin. The incidence of multidrug resistance TB is on the rise, and about 6.2% of MDR patients have been documented to have extensively drug-resistant tuberculosis (XDR). This issue is increasing the morbidity and mortality, and also XDR TB is difficult to treat. The treatment regime conventionally included longer regime with multiple drugs which had substantial side effects. Delamanid is a newer antitubercular drug which has been documented to have a role in effective treatment of XDR including shortening the tedious treatment period, but there is lack of evidence from our country. We present our early experience of use of delamanid in XDR tuberculosis.

Access this article online

Quick Response Code:

Website: www.lungindia.com

DOI: 10.4103/lungindia.lungindia_451_22

CASE 1

A 25-year-old male, non-smoker with no other co-morbidities initially reported at a peripheral hospital with history of cough and weight loss of 1 month duration. The cough was insidious in onset with mucoid expectoration and history of weight loss of 05 kilograms with reduced appetite and generalized malaise. On examination, he had bronchial breath sounds in left infraclavicular and interscapular area, and crackles were heard in right mammary area. On evaluation, there was thrombocytosis and raised erythrocyte sedimentation rate, with normal haemoglobin, liver and renal function tests. His chest radiograph showed dense acinar radiopacities in the left upper zone and superior part of Left middle zone, suggestive of active pulmonary tuberculosis [Figure 1a]. On sputum smear, Ziehl–Neelsen (ZN) stain 2+ acid-fast bacilli (AFB) were seen (RNCTP grading). He was diagnosed as sputum smear

How to cite this article: Marwah V, Patil PR, Choudhary R, Malik V. Early experience of delamanid in extensively drug-resistant pulmonary tuberculosis. Lung India 2023;40:75-8.

positive pulmonary tuberculosis and was initially started on first-line antitubercular drugs. He showed features of clinical deterioration with no weight gain, worsening of his chest radiograph and continued to be sputum smear positive even after one month of ATT. He was further evaluated at our centre, his sputum CBNAAT (gene Xpert) showed presence of Mycobacterium (MTB detected high), and rifampicin resistance was also present [Table 1]. His sputum MTB LJ medium culture showed positive growth for MTB with resistance to isoniazid, rifampicin, pyrazinamide, levofloxacin and ethambutol. The first-line probe assay (LPA-1) confirmed the rifampicin resistance (presence of rpoB mutation) and resistance to isoniazid (presence of katG mutation), while the second-line probe assay (LPA-2) showed fluoroquinolone resistance but sensitive to aminoglycosides. The patient was diagnosed as a case of pre-extensively drug-resistant tuberculosis and was started on bedaquiline-based therapy consisting of bedaquiline, linezolid, clofazimine, cycloserine and levofloxacin. However, he had suboptimal response and continued to have productive cough and radiological progression of disease even after 04 months of the above regime. In view of his worsening of disease, he was started on delamanid-based therapy. He showed significant clinical response in form amelioration of his cough and weight gain of 13 kilograms. He became sputum and culture negative after one month of delamanid therapy. His repeat chest radiograph showed significant improvement [Figure 1b]. His delamanid was stopped after 06 months, and he was discharged on continuation phase of ATT.

Case 2

A 34-year-old male with no previous known co-morbidities initially reported to a peripheral hospital with history of cough with mucoid expectoration, dyspnoea and weight loss of 14 kilograms in 1 month. On examination, he was cachectic (weight: 34 kilograms) and had pallor. The chest examination showed decreased expansion on right side with bronchial breath sounds on auscultation over right infra- and interscapular areas. On evaluation, he has anaemia (haemoglobin 9 mg/dl) and thrombocytosis, while rest of the biochemical parameters were within normal limits [Table 1]. He was also found to have positive hepatitis B antigen. His sputum ZN staining showed presence of AFB (2+), and sputum CBNAAT (gene Xpert) confirmed the presence of AFB but showed high-level rifampicin resistance. The chest radiograph showed non-homogenous opacity with extensive cavitary involvement of right upper and mid-zone [Figure 2a]. He was diagnosed as a case of sputum smear positive rifampicin-resistant pulmonary tuberculosis and was transferred to our centre for further management. At our centre, he underwent sputum LPA-1 which confirmed rifampicin and isoniazid resistance, and LPA-2 showed resistance to fluoroquinolone but sensitive to aminoglycoside. He was managed as case of pre-XDR tuberculosis and was started on bedaquiline-based ATT. He showed suboptimal response to the therapy and continued to be symptomatic with radiological

Table 1: Biochemical and microbiological investigations of the patients

Inv	Patient-1	Patient-2
Hb (gm/dl)	12.8	9
Platelets (/cmm)	5.40 lacs	5.60 lacs
Total bilirubin/ direct	0.4/0.1	0.5/0.1
OT/PT	32/38	30/42
Urea/Creatinine (mg/dl)	30/0.8	28/0.9
Sputum ZN stain	2+ AFB	2+AFB
Sputum CBNAAT	MTB detected high with rifampicin resistance present	MTB detected high with rifampicin resistance present
Sputum MTB C/s	MTB growth present with resistance to isoniazid, rifampicin, pyrazinamide, levofloxacin and ethambutol	MTB growth present with resistance to isoniazid, rifampicin, pyrazinamide and levofloxacin
Line Probe Assay-1	Rifampicin resistance (rpoB mutation) and isoniazid (KatG mutation) present	Rifampicin resistance (rpoB mutation) and isoniazid (KatG mutation) present
Line Probe Assay-2	Fluoroquinolone resistant and aminoglycoside sensitive	Fluoroquinolone resistant and aminoglycoside sensitive

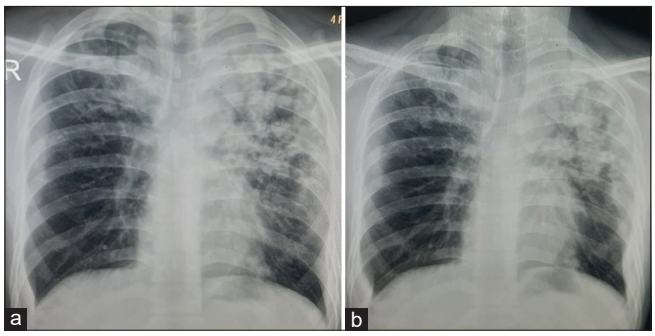

Figure 1: (a) Initial radiograph chest shows dense acinar radiopacities in the left upper zone, and superior part of left middle zone, suggestive of active pulmonary tuberculosis. (b) Radiograph chest obtained 04 months following institution of delamanid shows significant resolution of the lesions

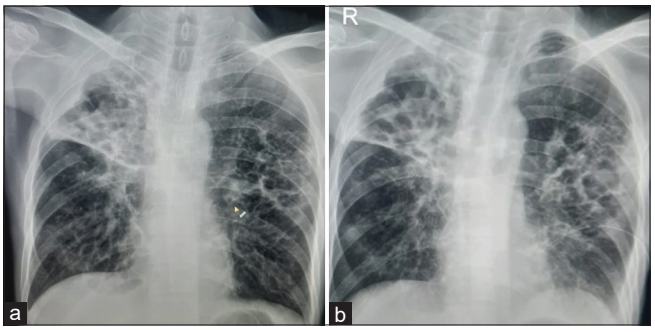

Figure 2: (a) Initial radiograph chest showing dense acinar radiopacities and cavitary lesions involving right upper zone, superior part of right middle zone and the left middle zone, suggestive of active pulmonary tuberculosis. (b) Radiograph chest obtained 05 months following institution of delamanid shows significant decrease in the lesions in the left middle zone

worsening. He also developed secondary spontaneous pneumothorax on right side which was managed with chest tube drainage, and later pleurodesis was also done with 2.5% povidone iodine. In view of clinical and radiological deterioration, delamanid was added to the therapy. The patient showed significant response to the ATT and attained smear conversion after two months and culture conversion after five months [Figure 2b]. Due to his extensive disease, the patient had developed post-tuberculosis sequelae which was confirmed by computed tomography of chest. His CT chest showed marked tubular, varicose and cylindrical bronchiectasis with bronchial wall thickening in segmental and subsegmental bronchi of all the lobes of both lungs with more conspicuous involvement of right upper and middle lobes. There were areas of consolidation on both sides. The spirometry showed mixed defect-moderate restriction (FVC-3.76 L (53.8%) and obstruction (FEV1/FVC-50.2%), FEV1-3.23L (46.6%). His DLCO was reduced suggestive of mild diffusion defect. The patient was given 06 months of bedaquiline and delamanid and was later continued continuation phase of ATT with total duration of ATT for 18 months.

DISCUSSION

Tuberculosis (TB) is the leading cause of death from an infectious disease globally. It is caused by Mycobacterium tuberculosis (MTB) which is a species of pathogenic bacteria in the family Mycobacteriaceae. There is increase in number of resistance cases to the conventional Tb drugs which is reducing the effectiveness of treatment regime of TB and is also affecting the national TB control. There is an unmet need of newer effective TB drugs with good safety profiles to turn the tide. Delamanid is one of the new antitubercular drugs developed in the last 40 years. It was developed by Otsuka pharmaceutical company as a part of their TB drug development programme.[1] It received its first global approval in the European Union (EU) on 28 April 2014, for use in combination with an optimized background anti-TB regimen (OBR) in patients with multidrug-resistant (MDR) TB.[2,3] It has since been approved by several other countries/regions for treatment of extensively drug-resistant TB cases.

Delamanid is a dihydro-nitroimidazooxazole derivative. It inhibits the synthesis of mycobacterial cell wall components, methoxy mycolic acid and ketomycolic acid. Delamanid is a pro-drug which gets activated by the enzyme deazaflavin-dependent nitro reductase. A reactive intermediate metabolite, formed between delamanid and desnitro-imidazooxazole derivative, is considered to play a vital role in inhibiting mycolic acid production.[3,4] Delamanid possesses potent activity against replicating, dormant and intracellular MTB bacilli and is bactericidal.[5,6] Delamanid is primarily metabolized by albumin in serum and much less by cytochrome P450 enzymes; it neither inhibits nor induces P450.[7,8]

In a 2-month randomized placebo-controlled clinical trial conducted on HIV-negative MDR-TB patients, delamanid was administered along with World Health Organization (WHO)-approved optimized background regimen (OBR). Sputum-culture conversion with MGIT by two months in the group of patients who received delamanid at a dose of 100 mg twice daily was 45.4%, compared with 29.6% in the placebo group (53%; 95% CI, 11 to 112; $P = 0.008$).[9] Long-term treatment with delamanid and a 24-month observational study was done as a continuation of the previous short-term trial to find out the treatment outcome. Patients who received delamanid for ≥6 months had more favourable outcomes than those who received ≤2 months of treatment. There was a significant reduction in mortality in the long-term delamanid-treated group. This analysis suggests that treatment with delamanid for six months in combination with an optimized background regimen can improve outcomes and reduce mortality among patients with both multidrug-resistant and extensively drug-resistant TB.[4,10]

The most common adverse events associated with delamanid include nausea (38%), vomiting (33%) followed by dizziness (30%).[11] A serious safety concern with delamanid is QTc interval prolongation. This effect was dose dependent as it was seen more frequently in the 200 mg BD/day group than in the 100 mg BD/day group.[9] This QT prolongation was found to have an association with hypoalbuminemia. Delamanid should be stopped if the QT interval is more than 500 ms.[11]

In our experience, both of our patients were case of multidrug-resistant tuberculosis and had suboptimal response to even bedaquiline-based therapy. Our patients were started on delamanid, and they have shown significant clinical and radiological response. Our centre is government-recognized drug resistant TB centre, so all the TB drugs including bedaquiline and delamanid are being procured through district TB centre. These patients did not have any side effects and tolerated ATT as well. There has been hardly any reported real-time experience of using delamanid in drug-resistant cases from India. Our study gives an important insight of use delamanid in multidrug resistant TB cases which needs to be validated with more numbers of patients in our country.

Declaration of patient consent

Written informed consents were obtained, and the study was performed in accordance with the principles of the Declaration of Helsinki.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Liu Y, Matsumoto M, Ishida H, Ohguro K, Yoshitake M, Gupta R, *et al*. Delamanid: From discovery to its use for pulmonary multidrug-resistant tuberculosis (MDR-TB). Tuberculosis 2018;111:20-30.
2. The Use of Delamanid in the Treatment of Multidrug-Resistant Tuberculosis: Interim Policy Guidance. Geneva: World Health Organization; 2014.
3. Xavier AS, Lakshmanan M. Delamanid: A new armor in combating drug-resistant tuberculosis. J Pharmacol Pharmacother 2014;5:222-4.
4. Skripconoka V, Danilovits M, Pehme L, Tomson T, Skenders G, Kummik T, *et al*. Delamanid improves outcomes and reduces mortality in multidrug-resistant tuberculosis. Eur Respir J 2013;41:1393-400.
5. Gengenbacher M, Duque-Correa MA, Kaiser P, Schuerer S, Lazar D, Zedler U, *et al*. NOS2-deficient mice with hypoxic necrotizing lung lesions predict outcomes of tuberculosis chemotherapy in humans. Sci Rep 2017;7:8853.
6. Chen X, Hashizume H, Tomishige T, Nakamura I, Matsuba M, Fujiwara M, *et al*. Delamanid kills dormant mycobacteria *in vitro* and in a Guinea pig model of tuberculosis. Antimicrob Agents Chemother 2017;61:e02402-16.
7. Upton AM, Cho S, Yang TJ, Kim AY, Wang Y, Lu Y, *et al*. *In vitro* and *in vivo* activities of the nitroimidazole TBA-354 against Mycobacterium tuberculosis. Antimicrob Agents Chemother 2015;59:136-44.
8. Pang Y, Zong Z, Huo F, Jing W, Ma Y, Dong L, *et al*. *In vitro* drug susceptibility of bedaquiline, delamanid, linezolid, clofazimine, moxifloxacin, and gatifloxacin against extensively drug-resistant tuberculosis in Beijing, China. Antimicrob Agents Chemother 2017;61:e00900-17.
9. Gler MT, Skripconoka V, Sanchez-Garavito E, Xiao H, Cabrera-Rivero JL, Vargas-Vasquez DE, *et al*. Delamanid for multidrug-resistant pulmonary tuberculosis. N Engl J Med 2012;366:2151-60.
10. Mok J, Kang H, Hwang SH, Park JS, Kang B, Lee T, *et al*. Interim outcomes of delamanid for the treatment of MDR- and XDR-TB in South Korea. J Antimicrob Chemother 2018;73:503-8.
11. Karekar SR, Marathe PA. Current status of delamanid in the management of MDR tuberculosis. J Assoc Physicians India 2018;66:72-5.