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REVIEW ON DELAMANID: A NEW EMA APPROVED DRUG FOR MULTI-DRUG RESISTANT TUBERCULOSIS

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Abstract:

Tuberculosis is emerging globally with an estimated prevalence of 8.7 million cases annually and 1.4 million deaths. The disease is caused by Mycobacterium tuberculosis. Since it is highly drug recessive, treatment is at the peak of threat and development of drugs against multi-drug resistant TB is still in progress. Management of tuberculosis seems more challenging when the patient develops drug resistant TB and with coexisting HIV. Despite the rise in incidence of MDR-TB worldwide over the past few decades, no TB specific drug has been discovered in last 40 years. Emergence of some new anti-tubercular drugs is a scope as they promise high efficiency and shortens the duration of treatment. Delamanid is one of such promising drug. High potency, least chance of drug-drug interactions, better toxicity profile, and post antibiotic effect against intracellular bacilli are the advantages with Delamanid which will be helpful in reducing the treatment duration and risk of toxicity in MDR-TB. Delamanid appeared to be a safe drug with less side effects. EMA has issued a conditional marketing authorization for Delamanid. It should be used as a part of an appropriate combination regimen for pulmonary MDR-TB in adult patients in whom the current approved regimen cannot be used because of resistance or intolerability. The emergence of this new drug can improve treatment status of TB and thus a hope for the better control of the disease.

Key Words: *Mycobacterium, Anti-Tubercular drugs, Delamanid, MDR- TB*

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INTRODUCTION:

Tuberculosis (TB), an ancient lethal infectious disease caused by 'Mycobacterium tuberculosis' is emerging globally with an estimated prevalence of 8.7 million TB cases annually and 1.4 million deaths. Tuberculosis [TB] remains a leading infectious killer globally which can produce either a silent or latent infection or a progressive disease. Tuberculosis (TB) is the most prevalent communicable infectious disease on earth and remains out of control in many developing nations. Left untreated or improperly treated, TB causes progressive tissue destruction and eventually death. TB remains out of contrast in many developing countries to the point that one-third of the world's population currently infected. Estimates suggest that one person dies of TB in India each minute. Giving increasing drug resistance, it is critical that a major effort be made to control TB before the most effective drugs are lost permanent. TB rates generally have rises with increasing urbanization and overcrowding because it is easier for an airborne disease to spread when people are packed closely together [1].

Directly Observed Treatment Strategy (DOTS) and Stop TB programs have substantially contributed to effectively improve the TB burden but rapid emergence of Mycobacterium resistant to anti tubercular drugs and rising cases of Human Immunodeficiency Virus (HIV) co-infection with TB in last few decades has come up as a real threat in effective management of tuberculosis. Rising trend of Multidrug resistant tuberculosis (MDR-TB) has been observed in European and Asian countries with 9-32% new cases and 50% previously treated cases being affected. Sensitive tubercular organisms respond well to the conventional treatment regimens as given by World Health Organisation (WHO).The standard regimen is capable of curing 85% cases but being cumbersome and lengthy; it fails to result in complete compliance by majority of patients. Moreover, not all the first line drugs are capable against persistent bacteria. Latent TB is treated with Isoniazid for 6-9 months where again patient compliance is a big question mark.

Management of tuberculosis seems more challenging when the patient develops drug resistant TB and HIV coexisting with TB. Despite the rise in incidence of MDR-TB worldwide over the past few decades, no TB specific drug has been discovered in last 40 years. So, in the current scenario of rising trend of resistant tuberculosis and AIDS co-infection with TB, a novel anti-tubercular drug is a prime need to decrease the disease burden. After such a long waiting period, revival in research and development activity in this area has resulted in discovery of a new anti-tubercular drug Delamanid (OPC-67683) [2].

DELAMANID FOR MULTI DRUG RESISTANT PULMONARY TUBERCULOSIS

CHEMISTRY

Delamanid(OPC-67683) is a drug in the nitroimidazole class with IUPAC name (2*R*)-2-Methyl-6-nitro-2-[(4-{4-[4-(trifluoromethoxy)phenoxy]-1-piperidinyl}phenoxy)methyl]-2,3-dihydroimidazo[2,1-b][1,3]oxazole

MECHANISM OF ACTION

Nitroimidazoles kill the bacteria in two ways

- By blocking the synthesis of mycolic acids (i.e., stopping the bacteria from creating building blocks important for their cell walls
- By poisoning them with nitric oxide, which the drugs release when metabolized [4].

PHARMACOKINETICS

It is advised to take delamanid along with food since the absorption gets better with food, in contrast to the first-line anti-TB drugs which should be taken on empty stomach. After oral administration, the maximum concentration is observed at 4-5 h. The half-life is 38 h after drug discontinuation. Steady-state concentration is reached after 10-14 days. In early trials, delamanid exposure was not found to be proportional to the dosage and it plateaued at 300 mg. This might be due to the poor water solubility of the drug and the limited absorption at higherdoses [2,6].

PRE-CLINICAL STUDIES

In in-vitro studies, Delamanid showed more potent antibacterial activity against drug-susceptible and drug-resistant strains of M. tuberculosis. The minimum inhibitory concentration was observed in an extremely lower range of 0.006-0.024 µg/ml. Post antibiotic effect on intracellular organisms had been demonstrated after pulsed therapy, which was comparable with that of Rifampicin. There was no cross-resistance and antagonist effect was observed with first-line anti-TB drugs. Delamanid was devoid of mutagenicity in bacterial reverse mutation test. High therapeutic efficacy with quicker eradication of tubercular bacilli was demonstrated in experimental mouse models [3].

CLINICAL TRIALS

Early bactericidal activity: Early bactericidal activity of different doses of Delamanid was demonstrated in smear-positive TB patients (n = 48) by reduction in colony-forming units (CFU) of M. Tuberculosis. The treatment duration was 14 days. Increased reduction in CFU was observed with 200 mg/day and 300 mg/day doses.

Delamanid showed monophasic bactericidal activity in contrast to Rifampicin and Isoniazid which
Showed biphasic activity [2].

Short-term trial: 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). Higher sputum culture conversion rates were observed in the treatment group compared to patients on placebo and background regimen.

Long-term trial: Long-term treatment with Delamanid and a 24-month observational study was done as a continuation of previous short-term trial to find out the treatment outcome. Patients who received Delamanid for ≥6 months had more favorable outcome than the patients who received ≤2 months of treatment. There was significant reduction in mortality in the long term Delamanid group.

ADVERSE EFFECTS
The incidence of QT prolongation was observed to be significantly higher in the treatment group compared to the placebo group. This effect was observed to be dose dependent as it was seen frequently in 200 mg BD/day group than in 100 mg BD/day group. However, it was of mild to moderate severity and not associated with symptoms of syncope and arrhythmia. No other serious treatment emergent adverse effects had been observed in the clinical trials [4].

DRUG INTERACTIONS
In-vitro studies showed that the drug is not metabolized by cytochrome P450 (CYP 450) enzymes [3]. No significant interactions were observed between Delamanid and anti-retroviral drugs such as Tenofovir, Lopinavir/Ritonavir, and Efavirenz in healthy subjects[6]. This is a desired property, as other anti-TB drugs can be combined with Delamanid without any fear of drug interactions.

CURRENT STATUS
EMA has issued a conditional marketing authorization for Delamanid (Deltyba, 50 mg tablet). It should be used as a part of an appropriate combination regimen for pulmonary MDR-TB in adult patients in whom the current approved regimen cannot be used because of resistance or intolerability. [7]

ADVANTAGES AND LIMITATIONS
High potent action, least chance of drug-drug interactions, better toxicity profile, and post antibiotic effect against intracellular bacilli are the advantages with Delamanid which will be helpful in reducing the treatment duration and risk of toxicity in MDR-TB. Long-term clinical trials on the safety and efficacy, interaction studies with standard and newer anti-TB agents, pharmacokinetic studies in special populations, and studies on drug administration with food need to be conducted in future.
The European Medicines Agency (EMA) recommended conditional marketing authorization for Delamanid in adults with multidrug-resistant pulmonary tuberculosis without other treatment options because of resistance or tolerability.

CLINICAL STUDIES
In a randomized, placebo-controlled, multinational clinical trial, 481 patients (nearly all of whom were negative for the human immunodeficiency virus) with pulmonary multidrug-resistant tuberculosis were assigned to receive Delamanid, at a dose of 100 mg twice daily (161 patients) or 200 mg twice daily (160 patients), or placebo (160 patients) for 2 months in combination with a background drug regimen developed according to World Health Organization guidelines. Sputum cultures were assessed weekly with the use of both liquid broth and solid medium; sputum-culture conversion was defined as a series of five or more consecutive cultures that were negative for growth of *M. tuberculosis*. The primary efficacy end point was the proportion of patients with sputum-culture conversion in liquid broth medium at 2 months.

RESULTS:
Among patients who received a background drug regimen plus 100 mg of delamanid twice daily, 45.4% had sputum-culture conversion in liquid broth at 2 months, as compared with 29.6% of patients who received a background drug regimen plus placebo (P=0.008). Likewise, as compared with the placebo group, the group that received the background drug regimen plus 200 mg of delamanid twice daily had a higher proportion of patients with sputum-culture conversion (41.9%, P=0.04). The findings were similar with assessment of sputum-culture conversion in solid medium. Most adverse events were mild to moderate in severity and were evenly distributed across groups. Although no clinical events due to QT prolongation on electrocardiography were observed, QT prolongation was reported significantly more frequently in the groups that received delamanid.

EFFICACY OF DELAMANID
EMA approval was based primarily on a two-month, phase II study involving 481 people with drug resistant TB (including both MDR-TB and XDR-TB). Participants were randomized to three arms: Delamanid at 100 mg twice daily plus other

available drugs in an optimized background regimen (OBR); Delamanid at 200 mg twice daily plus an OBR; or placebo plus an OBR. This study found that:

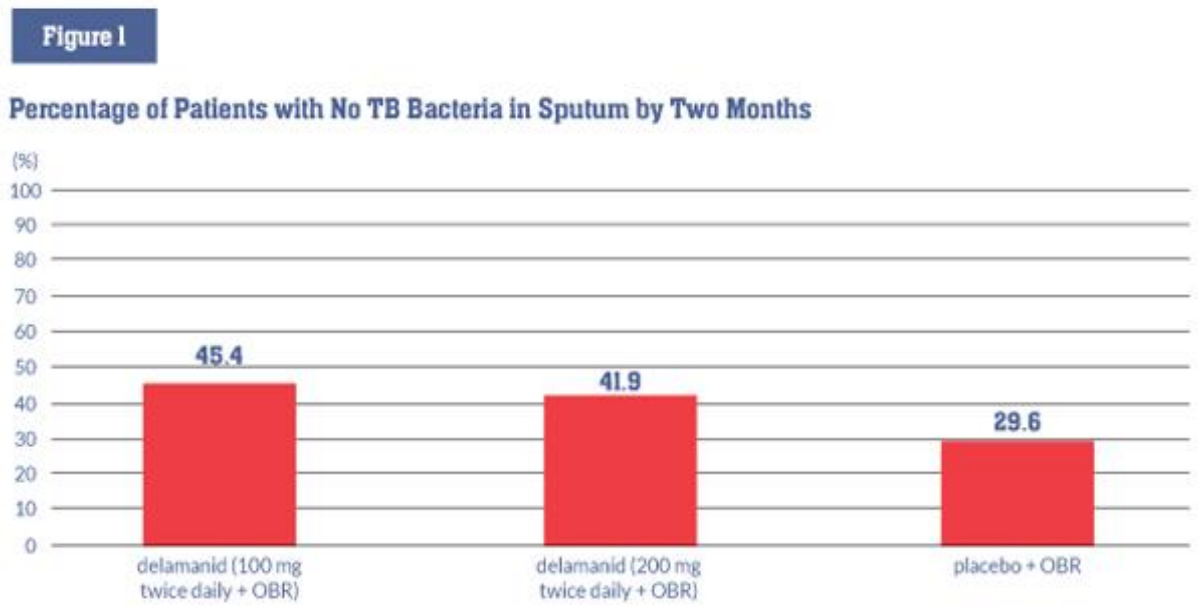
- Delamanid, given for two months with an OBR, increased by 16 percent the proportion of people who no longer had cultures of sputum that grew M. tuberculosis, the bacterium that causes TB disease (also known as sputum culture conversion) (45.4% vs. 29.6%, P = .008). This is an important sign that treatment is working (see figure 1); [5]
- Delamanid, when given with an OBR, reduced the time required to achieve sputum
- culture conversion (cultures became negative faster); and [6]
- Delamanid did not appear more effective when given at 200 mg rather than 100 mg twice daily [7].

After this study finished, surviving participants could choose to enter a six-month extension study, where their doctors could choose to give them Delamanid at either 100 mg or 200 mg.[8] Time gaps between inclusion in the two-month and the six-month studies varied widely, with over one-third of participants waiting four months or more. Thus, some got Delamanid for six months (if they had not gotten it in the two-month study), some got it for eight months with a break in the middle, and those who did not participate in the six-month study got Delamanid for either two months or not at all.

The EMA decided to look at the follow-up data from as many people as possible who participated in the first or both studies. Two years after starting treatment, 75 percent of those who received Delamanid for six months or more had no bacteria in their sputum (participants who chose the six-month study),[9] compared with 55 percent who received Delamanid for two months or less (participants who did not choose the six-month study). Only one percent of those who received long-term Delamanid died, versus 8.3% of those who got two months of no Delamanid (P < .001).[10] However, the confusing study design, with many losses to follow-up, drop-outs, and deaths, makes it hard to know if these differences were due to Delamanid or other factors, and the best dose and length of treatment remain unclear [10].

Delamanid's phase III trial completed enrolment in late 2013, but given the long treatment and follow-up time required for TB trials, results may take years to become available. This trial, which gives Delamanid at 100 mg twice daily for two months, and then at 200 mg once daily for four months (which should simplify dosing), will provide more data on the long-term efficacy of the drug. In the meantime, the randomized, two-month trial data show clearly that Delamanid is effective at killing TB bacteria in people with MDR-TB, and the available longer-term data, though flawed, point to possible improvements of long-term treatment outcomes and survival.

Figure 1



Note: The differences between the Delamanid 100 mg and 200 mg groups and the placebo group were statistically significant (P = .008, and P = .04).

SAFETY OF DELAMANID

Side effects and mortality

Delamanid appears to be a mostly safe drug with manageable side effects. Available data are insufficient to prove beyond a doubt an effect on mortality, due to confounding factors in the six-month study.

Delamanid's most common side effects are:

- nausea, vomiting, and dizziness (in about one- third of people taking it);
- low potassium levels in the blood; and
- Paresthesia (a pricking or tingling sensation), anxiety, and tremor (shaking) [11].

Delamanid's most serious side effect is QT prolongation, a disturbance in the heart's electrical activity that can lead to serious heart rhythm disturbances, such as ventricular tachycardia, and sometimes to sudden death. However, in the studies to date, no clinical events occurred as a result of this prolongation. Other than QT prolongation, the risk of having a serious side effect was about the same for patients receiving delamanid or placebo in the two-month trial. Delamanid did appear to have fewer side effects when given at 100 mg rather than 200 mg twice daily [12,13].

Safety and effectiveness to use with other TB drugs

Delamanid appears not to interact with most other TB drugs, though giving Delamanid and Ethambutol together increased the amount of Ethambutol in the body by about 25 percent.

QT prolongation, the most troubling side effect of Delamanid, is also caused by other MDR-TB drugs like Bedaquiline, Clofazimine, and Moxifloxacin. For patients with extensive drug resistance and limited treatment options, potential benefits of combining two or more of these drugs may outweigh potential risks, particularly when regular monitoring for heart safety (i.e., electrocardiograms, or ECGs) is available [14].

Safety and effectiveness to use with HIV medicines

Delamanid has not been studied in people with HIV taking anti-retrovirals. In a study of healthy participants, Delamanid did not significantly affect the levels of Tenofovir, Lopinavir/Ritonavir, or Efavirenz in the body, though Lopinavir/Ritonavir did increase the amount of Delamanid in the body by 20 percent.15,16 When the body breaks down Delamanid, one particular molecule, DM-6705, appears to cause QT prolongation. Lopinavir/ritonavir seems to increase the amount of DM-6705 in the body by about 30 percent, and the EMA recommends frequent ECG monitoring if Delamanid and Lopinavir/Ritonavir are taken together [17].

Safety for children, pregnant women, or nursing women

Delamanid is currently in clinical trials for children ages six to 17 (children from birth to age six will be enrolled once safety data on older children and the pediatric formulation's bioequivalence are available) [18,19].

While the trial is ongoing, the drug is recommended for adults only. In some circumstances, potential benefits may outweigh potential risks: Delamanid has been given successfully to one 12-year-old child. Delamanid is not recommended for pregnant women, as animal studies have shown some toxicity to the fetus (when Delamanid was given to pregnant rabbits at toxically high doses) [20,21].

However, it is also harmful to the fetus to have a mother who is very sick with TB. There may be circumstances (e.g., when other treatments are not effective, available, or tolerable) in which a pregnant woman decides that the potential benefit of taking Delamanid outweighs the potential risk. Pregnant women have an absolute right to treatment and must be allowed to make informed decisions about their care in consultation with their doctors. It is unknown if Delamanid is passed through human breast milk, so nursing mothers taking Delamanid should consider discontinuing nursing.

EMA approval

Given the urgent need for new medicines to treat MDR-TB, the EMA granted approval based on the limited available data for Delamanid for pulmonary MDR-TB (MDR-TB of the lungs) in adults for whom an effective treatment regimen cannot otherwise be constructed due to resistance or tolerability. The recommended dose is 100 mg twice daily, given for six months, in addition to other MDR-TB medicines. This approval of Delamanid is conditional, meaning that Otsuka (the company that makes Delamanid) must complete additional studies to maintain Delamanid's approvals (see table 1). Although the approval is for pulmonary MDR-TB, there is no reason to believe that the drug would not be effective in extrapulmonary MDR-TB (MDR-TB outside of the lungs).

Table 1: Activities required by the EMA as a Condition of Delamanid's Approval

Requirement	Purpose	Deadline
Pediatric investigational plan*	Study the pharmacokinetics and safety of delamanid in children ages 0–18 (given for 10 days at 100 mg twice daily for children 12 and older, and 50 mg twice daily for children under 12, and then a six-month extension of that study to evaluate long-term safety and efficacy) and demonstrate bioequivalence of a pediatric dispersible formulation to the adult tablets	April 2017
Phase III trial	Confirm delamanid's safety and efficacy when given for six months (100 mg twice daily for two months, followed by 200 mg once daily for four months) at the beginning of 18–24 months of treatment with other MDR-TB drugs	First half of 2017
Dosing study	Find the best dose of Delamanid by comparing Delamanid at 100 mg twice daily for two months, followed by 200 mg once daily for four months, with Delamanid at 400 mg once daily	End of 2018

*Note: The EMA determined requirements for Delamanid's pediatric investigational plan in advance of Delamanid's approval [18, 19].

CONCLUSION:

Recent approval of the anti-TB drug Delamanid provides scope in managing drug-resistant TB.

The desirable properties of good efficacy, least toxicity, and absence of interaction with antiretroviral drugs might make Delamanid an important option in treating MDR-TB, XDR-TB, and TB in HIV-positive individuals. But to mark it superior to existing drugs for drug sensitive, latent, extra pulmonary TB and TB HIV co-infection, more exploratory trials are needed to be conducted in future. Delamanid was not associated with an increase in mortality compared with placebo such as was seen with Bedaquiline (another new anti-tubercular drug) in phase II trials. The phase III trial to confirm Delamanid's safety and efficacy in a long term, better-designed trial is completely enrolled.

More data are available to support the safety and efficacy of these drugs against TB than there are for other MDR-TB drugs in trial. Patients with MDR-TB that is difficult to treat, such as pre-XDR-TB and XDR-TB, or intolerance to older drugs, need better options as soon as possible

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