Delamanid: A new armor in combating drug-resistant tuberculosis

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ABSTRACT

Intense search has been made in the discovery of newer anti-TB drugs to tackle the issues such as drug resistance, HIV co-infection and risk of drug-drug interactions in the management of TB. Delamanid, a newer mycobacterial cell wall synthesis inhibitor, received a conditional approval from European medicines agency (EMA) for the treatment of MDR-TB. Preclinical and clinical studies have shown that delamanid has high potency, least risk for drug-drug interactions and better tolerability.

Key words: Delamanid, multidrug-resistant tuberculosis, mycolic acid inhibitor

INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB) is the development of resistance to rifampicin and isoniazid in *Mycobacterium tuberculosis* infection. If the resistance extends to second-line anti-TB drugs such as fluoroquinolones and an injectable drug, then it is called as extensively drug-resistant TB (XDR-TB). In India and other South Asian countries, totally drug-resistant TB has been often reported recently.[1] Treating these drug-resistant TB conditions is a challenging task because of longer duration of treatment, vulnerability to drug interactions, toxicity, and the burden caused by the cost of treatment. Moreover, co-existence of TB in immunosuppressed conditions such as AIDS and malnutrition, and increased incidence of MDR and XDR-TB in such situations are frequent. Hence, it is well speculated that these issues are the most important hindrances towards achieving TB-free society. Therefore, there is an unmet need to develop drugs acting via novel targets with better efficacy with least chance for drug interactions and a desirable toxicity profile. To combat these problems, newer targets and drugs against TB are being explored and many newer drugs are in the pipeline of development. The new drug delamanid received conditional approval by European Medicines Agency (EMA) for the treatment of MDR-TB in November 2013.

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MECHANISM OF ACTION

Delamanid is a dihydro-nitroimidazooxazole derivative. It acts by inhibiting 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 nitroreductase (Rv3547). A reactive intermediate metabolite, formed between delamanid and desnitro-imidazooxazole derivative, is considered to play a vital role in the inhibition of mycolic acid production.

PHARMACOKINETICS

It is advised to take delamanid along with food since the absorption gets better with food, in contrast to the first-line

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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.[2] 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 higher doses.

PRECLINICAL 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.[4]

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 treated group.[5]

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.[4] 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.

DRUG INTERACTIONS

In vitro studies have shown that drug is neither metabolized by cytochrome P450 (CYP 450) enzymes nor influences the enzymes at the expected therapeutic concentrations.[3] In clinical trials conducted on healthy subjects, no significant interactions were observed between delamanid and anti-retroviral drugs such as tenofovir, lopinavir/ritonavir, and efavirenz.[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.

CONCLUSION

Recent approval of anti-TB drugs such as bedaquiline and delamanid has boosted our confidence 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.

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