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Delamanid- A ray of hope for drug resistant tuberculosis

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Abstract

The emergence of drug-resistant tuberculosis is a major threat to tuberculosis care and control throughout the world. The lack of effective, affordable and safe drugs for the treatment of MDR-TB is a key factor in the inability of programs to boost up their treatment efforts to meet national and global targets. Delamanid, a newer mycobacterial cell wall synthesis inhibiting drug, received a conditional approval from European medicines agency for the treatment of MDR-TB. Delamanid, in addition to its previously demonstrated efficacy in pulmonary tuberculosis, might be an effective therapeutic approach to treating extra pulmonary tuberculosis. Treatment with Delamanid for 6 months in combination with an optimized regimen can improve patient outcomes and reduce mortality and morbidity among patients with both multidrug-resistant (MDR) and extensively drug-resistant TB (XDR).

Keywords: Delamanid; Efficacy; MDR-TB; Tuberculosis

Introduction

Tuberculosis (TB) is an infectious disease caused predominantly by mycobacterium tuberculosis. TB is most commonly transmitted by droplet route, when a patient coughs or sneezes. Tuberculosis usually affects lung, but can also affect lymph node, pleura, bone, joint, genitals, nervous system, skin or abdomen. The diseases like HIV AIDS and TB constitute the top two killers among all the infectious diseases especially in developing countries like India [1].

Drug resistant TB (DR-TB) is a severe form of Tuberculosis. In 2015, there were an about 480000 new cases of multidrug-resistant TB (MDR-TB) and an additional 100 000 people with rifampicin-resistant TB (RR-TB) who were also classified as MDR TB. Drug resistance surveillance data shows that 3.9% of new and 21% of previously treated TB cases was estimated to have had rifampicin or multidrug-resistant tuberculosis (MDR/RR-TB) in 2015 [1].

Presently 2nd line antitubercular drugs, Pyrazinamide, Ethambutol and new mycobacterial ATP synthase inhibitor, Bedaquiline [2] are used for treatment of drug resistant TB. Treatment of MDR-/XDR-TB is pretty difficult for both patients and healthcare personnel, due to the long duration of treatment, the cost of expensive regimens, poor drug tolerability associated with frequent adverse events, poor compliance and a high treatment failure rate [3-10]. Consequently, as of today not all diagnosed MDR-TB cases have had access to quality treatment [11]. The difficult task for any physician dealing with MDR-TB is to ensure the minimum number of drugs necessary to design an effective regimen

The new drug Delamanid received conditional approval by European Medicines Agency for the treatment of MDR-TB in November 2013. Delamanid (previously known as OPC-67683) is a dihydro-nitroimidazooxazole derivative belonging to the class of nitroimidazoles. It was developed and produced by Otsuka Pharmaceutical Development and Commercialization (Osaka, Tokyo, Japan) [12]. During the course Delamanid showed a splendid in-vitro and in-vivo activity, being efficacious against both extra- and intracellular mycobacteria. Although there are few other drugs in this class, Delamanid is the first drug in its class to reach approval and clinical use.

Criteria for Delamanid addition [13]

A pre-defined questionnaire, PICO (Population, Intervention, Comparator, Outcome) used in consultation with the WHO Expert Group: "*In MDR-TB patients, does the addition of Delamanid to a background regimen based on WHO-recommendations safely improve patient outcomes?"*

For systematic research of Delamanid, PICO comprises four elements:

- Population: targeted by the action/intervention: patients with MDR-TB, including newly diagnosed patients, patients treated empirically for MDR-TB, HIV-infected patients (+/- use of ARVs), and children;
- Intervention: addition of Delamanid during the first 6 months of WHO-recommended background MDR-TB therapy;
- Comparator: addition of placebo to WHO-recommended MDR-TB treatment;
- Outcome: efficacy (as demonstrated by sputum culture conversion during treatment and final treatment outcomes based on WHO definitions), safety (toxicity, serious adverse events, mortality).

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 an important role in the inhibition of mycolic acid production [14].

Pharmacokinetics

It is preferable to take Delamanid along with food since the drug get absorbed better with food, in contrast to the first-line anti-tubercular drugs which should be taken on empty stomach. After oral administration, the maximum concentration is observed at 4-5h. The half-life is 38 hours 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 higher doses.

Delamanid is metabolized by liver enzyme, cytochrome P450 (e.g. CYP3A4) and formation of its main metabolite is regulated by plasma albumin. It is neither an inducer nor an inhibitor of key drug metabolizing enzymes, so is unlikely to have a significant impact on concentrations of co-drugs.

Appropriate candidates for Delamanid treatment [13]

Based on the available research and recognizing the limits of available clinical data, the EG recommended that Delamanid (100mg BD for six months) may be added to a WHO recommended regimen in MDR-TB adult patients under specific conditions and taking into account the following remarks *(conditional recommendation, very low confidence in estimates of effects*):

- The population to whom this recommendation applies is MDR-TB patients. This may also include those with additional resistance or intolerance to fluoroquinolones or second line injectable drugs, those with extended lesions, advanced disease and others deemed at higher baseline risk for poor outcomes, as well as patients with XDR-TB.
- The population excludes patients with QT prolongation.
- Adherence to principles of designing a WHO-recommended regimen is required. As with all TB treatment regimens, Delamanid should never be added as a single drug to an already failing regimen. Rather, it should be part of a multi-drug regimen, in which the other companion drugs are selected based on WHO MDR-TB treatment guidelines.
- This recommendation includes PLHIV, as individuals with HIV co-infection were included in the RCT.
- Delamanid has not been tested in pregnant and breastfeeding women, children, and patients with extra-pulmonary MDR-TB, and there are limited or no data describing the effects of substance abuse, advanced age and diabetes. Because of uncertainty regarding safety and efficacy in these patient populations, particular precaution is suggested for use of Delamanid in these conditions.
- The use of the drug in patients with extra-pulmonary MDR-TB may be considered, extrapolating from the data in patients with pulmonary TB.

Drug interactions and adverse effects of Delamanid

TB is such an old disease and still prevalent despite several drugs, new classes of tuberculosis antibiotics are under development. The increasing prevalence of MDR-TB and XDR-TB, and the association between the TB and HIV epidemics is need of hour for more effective drugs. Drugs that act synergistically to rapidly eradicate mycobacterium TB infection and shorten treatment regimens do not interfere with the pharmacokinetics of other medications especially antiretroviral therapy (ART). Drugs that are active against dormant organisms, and will eradicate Latent tuberculosis infection would be more useful. When introducing Delamanid into a new regimen, there is also the potential for its interaction with other drugs administered concurrently, with additive or synergic adverse effects. Second line Anti TB drugs notably fluoroquinolones and Clofazimine, if co-administered with Delamanid may potentially increase the risk of cardiotoxicity. In ECG, 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.[15] However, it was of mild to moderate severity and not associated with symptoms of syncope and arrhythmia. No other serious adverse drug reaction had been observed in the clinical trials except nausea, vomiting, headache, etc.

The combination of Delamanid and Bedaquiline together, and, eventually, of other QT interval-prolonging drugs (e.g., fluoroquinolones, Clofazimine) is prone to adverse events and can lead to QT prolongation at dangerous levels. The recommendation to obtain and assess a baseline electrocardiogram (ECG) prior to starting the combination treatment and regularly repeat ECGs during treatment with such drugs to monitor the QT interval is important to prevent cardiac problems. ECG should be performed at baseline

and, then, at regular intervals (e.g., weekly on the first instance and in reduced frequency should QTc prolongation not manifest). Interestingly, the addition of Delamanid to MDR-TB treatment regimens improved outcomes [16]. Future trials combining Delamanid with other new drugs such as Bedaquiline and Moxifloxacin will improve on outcomes seen in the trials with PA-824, hopefully [17]. It is better not to be used for TB meningitis until it is known whether it penetrates the blood-brain barrier adequately. In extremely challenging M/XDR-TB cases, when the number of drugs is not enough to reach the recommended number of at least four to design an effective regimen, some clinicians have considered using Delamanid and Bedaquiline in combination.

Conclusions

Recent approval of Delamanid has boosted our confidence in managing DR-TB. The desirable properties of good efficacy, least toxicity and less interaction with antiretroviral and other antitubercular drugs might make Delamanid an important option in treating MDR-TB, XDR-TB and TB in HIV-positive individuals and to reduce the burdens of these difficult, costly, and life-threatening conditions. Besides, further research in to its wider usage is indicated.

Conflicts of interest: None

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