UPDATE ARTICLE

Current Status of Delamanid in the Management of MDR Tuberculosis

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Abstract

Delamanid is a nitro-dihydro-imidazooxazole compound which was developed by a Japanese company, Otsuka Holdings inc. and has shown in-vitro and in-vivo activity against drug resistant tuberculosis. The drug exerts its anti-mycobacterial activity by inhibition of mycolic acid biosynthesis, leading to defective cell wall formation ultimately leading to bacterial death. Following the promising results in Phase 2 trials, Delamanid received approval in European Union in 2014, following which it was also approved in Japan and Korea in the same year. It was approved in India recently in August, 2017. Though relatively well tolerated, there have been concerns due to QT prolongation associated with the use of Delamanid. WHO has currently recommended use of Delamanid in combination with optimized background regimen in patients with pulmonary TB (conditional recommendation). More data from clinical trials and observational studies is awaited regarding use of Delamanid in children, HIV co-infection, pregnant women and use in combination with Bedaquiline.

Introduction

Tuberculosis (TB) has been one of the leading causes of mortality and morbidity worldwide. It has been ranked among the top 10 causes of death globally by the World Health Organization (WHO).[1] In 2015, it was estimated to have caused 10.4 million new cases and 1.4 million deaths all over the world.[2] Out of seven countries accounting for 64% of the total TB burden, India is in the lead, followed by Indonesia, China, Philippines, Pakistan, Nigeria, and South Africa.[1] The emergence of Multidrug Resistant (MDR) and Extensively Drug Resistant(XDR) strains have made the treatment of TB more challenging. MDR TB is defined as resistance to both Isoniazid and Rifampicin.[3] XDR TB is defined as resistance to Isoniazid and Rifampicin, one of the fluoroquinolones and at least one of the second-line anti-TB injectable drugs.[4] In 2016, there were 600 000 new cases of Rifampicin resistant TB, of which 490 000 had MDR-TB.[1] Among the 30 countries which had the highest number of TB cases, 90% cases belonged to the MDR/RR TB category.[5] MDR TB accounts for approximately 4% of the new cases and 20% of the retreated cases of tuberculosis in India.[3] About 6.2% of MDR-TB cases in India had XDR-TB in 2016.[1]

The *WHO End TB strategy* which was approved by the World Health Assembly in 2014 aims to reduce TB deaths by 90% and TB incidence rate by 80% by 2030. Globally, though the incidence of TB is declining at about 2% per year however a targeted decline of 4–5% annually is needed to reach the End TB Strategy targets.[1] There is continuing research with eight new drugs and 12 vaccine candidates in the pipeline.[1] The current treatment regimens for MDR TB are lengthy, requiring at least five drugs to be given for a duration of 18-24 months.[6] They are also associated with a number of side effects and have shown a lower success rate, often less than 50%.[7,8] Currently only 54% of MDR-TB patients and 30% of XDR-TB have been treated successfully worldwide.[1] As a result of the drawbacks of the current MDR TB regimens, extensive research is being carried out in this domain and several new compounds have been discovered.[9] Delamanid is one such compound, which appears to be a promising addition to the current treatment regimen for MDR TB. This drug was recently approved by the Drug Controller General of India in August, 2017. In view of this development, it is pertinent to discuss the pharmacology, recent updates and current status of Delamanid in management of MDR TB.

History

In 1982, Akihiko Otsuka (former Chairman of Otsuka Holdings inc., Japan) initiated a programme to develop a new anti-TB agent that would be effective against both drug-susceptible and drug-resistant strains of M. tuberculosis. They focused on 6-nitro-2,3-dihydroimidazo[2,1-*b*] oxazoles (Nitroimidazoles), synthesized various compounds to enhance anti-tuberculosis activity, and carried out studies to eliminate mutagenicity and general toxicity. After investigating *in vitro* activity, acute *in vivo* efficacy, and the bacterial reverse mutation (BRM) test, compounds that passed the acceptance criteria were evaluated for *in vivo* efficacy in a chronic mouse model. Compounds that showed superior therapeutic efficacy in the chronic mouse model compared to Rifampicin were then evaluated for their safety profiles in rats. Otsuka's targeted strategy for screening new TB candidates has led to the discovery of Delamanid, which was subsequently validated and developed through preclinical and clinical studies.[10]

Mechanism of Action

Delamanid is a dihydro-imidazooxazole compound. ([2R]-2-methyl-6-nitro-2-[(4-{4-[4-(trifluoromethoxy)phenoxy]-1-

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piperidinyl}phenoxy)methyl]-2,3-dihydroimidazo[2,1-b][1,3]oxazole).[11] In *vitro*, Delamanid has shown mycobacteria specific antibacterial activity with no action on other gram positive or negative bacteria.[8] It exerts its anti-mycobacterial activity by inhibiting mycolic acid biosynthesis. Delamanid disrupts the cell wall of the mycobacterium and facilitates increased drug penetration through it. It is a prodrug that is activated by bioreduction of its nitro group by M. tuberculosis enzyme, deazaflavin-dependent nitroreductase to produce reactive species. The reactive intermediate such as nitrogen oxides formed between Delamanid and its desnitro- imidazooxazole derivative have been associated with significant mycolic acid synthesis inhibition.[12] Delamanid inhibits the keto mycolic and methoxy mycolic acid components of the cell wall but not the alpha mycolic acid.[5,8] However, alpha-mycolic acids are predominant components of mycobacterial cell wall followed closely by methoxymycolic acids, beta mycolic acid with significantly less contribution by ketomycolic acids.[13] Isoniazid inhibits the synthesis of the major mycolate component *viz* alpha-mycolic acid, methoxymycolic acid, and beta-mycolic acid. This may explain the difference in efficacy of both these drugs.

In vitro and In vivo Activity

Delamanid has been shown to exhibit very high anti-TB activity in comparison to other anti TB drugs, with a minimum inhibitory concentration (MIC) against standard drug susceptible and resistance strains of tuberculosis ranging between 0.006 microg/ml and 0.012 microg/ml. Moreover, these concentrations were between 2 and 512 times lesser than the MICs of established first line anti TB drugs.[9] The intracellular killing activity of 0.1 microg/ml of Delamanid was similar to that of 3 microg/ml of Rifampicin at a certain concentration, indicating more potent action of Delamanid.[9] A study by Matsumoto *et al* further substantiated that Delamanid exhibits the most potent bactericidal activity, similar to Rifampicin and superior to Isoniazid.[8] It also possesses *in vitro* activity against *M. kansasii* and M. *bovis* but not against M. *avium*, M. *chelonae*, M. *abscessus*, or M. *fortuitum*.[7] Thus, Delamanid showed promising results *in vitro* and *in vivo* studies against both drug susceptible and drug resistant strains, which led to its further development. Post antibiotic effect has been demonstrated in preclinical studies after pulsed therapy on intracellular organisms, which was comparable with that of rifampicin, which may be of additional benefit in increasing the efficacy of treatment of MDR-TB[14]

Pharmacokinetics

As opposed to the other first line drugs which are to be taken on an empty stomach, Delamanid is to be taken along with food as its absorption increases with food.[12] The oral availability of the drug is 2.7 times higher in fed state as compared to fasting state. The peak plasma concentrations are obtained at 4 hrs after administration.[9] Delamanid and its metabolites exhibit high plasma protein binding (>99%). It has a large volume of distribution of around 1,100 litres after 100 mg twice daily oral administration.[9] Delamanid is primarily metabolised rapidly to a metabolite DM-6705 by a reaction between the amino acid groups present in albumin and the 5-C of 6-nitro-2,3-dihydroimidazo[2,1-b]oxazole moiety of Delamanid. Some metabolism occurs via liver microsomal Cytochrome (CYP) 450 3A enzyme.[9] Four major metabolites(M1-M4) of Delamanid have been identified. These metabolites have limited anti-mycobacterial activity however they may contribute to QT prolongation.[7] Delamanid has a plasma half-life ranging between 30 to 38 hours, while its metabolites have a half-life ranging between 122-322 hours.[9] Steady state concentrations are reached 10-14 days after administration.[14] It is excreted primarily via faecal route, urinary excretion being less than 5%.[9] No dose modifications are required in mild to moderate renal impairment, but data regarding severe renal impairment is not available. Though it can be used in mild hepatic insufficiency, it should be avoided in moderate to severe liver disease.[15]

Dosage and Administration

Currently, Delamanid has been recommended to be used orally at a dose of 100 mg twice daily for 24 weeks. It has to be administered with optimized background regimen and has shown to improve the sputum conversion and decrease mortality in patients with MDR TB.[16] It is recommended to be administered as directly observed therapy.[15] At present its use is limited at a few centres in India.

Adverse Events and Monitoring

The most commonly adverse events associated with Delamanid include nausea(38%), vomiting(33%) followed by dizziness(30%).[15] A dose dependent QT prolongation was observed in the Delamanid group as compared to placebo in phase II trials. This QT prolongation was found to have an association with hypoalbuminemia. The QT prolongation was not associated with arrhythmia or syncope. It is recommended that electrocardiography is to be done at 2 weeks, 12 and 24 weeks and Delamanid should be stopped if QT interval is more than 500ms.[17] Also, serum potassium, calcium and magnesium levels need to be monitored in view of concerns regarding QT prolongation. However, there was no significant difference between Delamanid and placebo groups with respect to occurrence of overall serious adverse events.[11]

Drug Interactions

Delamanid has not been shown to be a substrate for P- glycoprotein transporter. At therapeutic concentrations, it is unlikely to have any clinically significant interactions with drugs metabolised via CYP enzymes.[9] Delamanid was studied in a trial involving healthy volunteers at a dose of 200 mg daily dose with and without Rifampicin (300mg daily)/ Isoniazid (720mg daily)/Pyrazinamide (1800mg daily) or Ethambutol (1100mg daily) for 15 days. Concomitant use of Delamanid did not change the levels of all the first line drugs except Ethambutol which showed increased plasma concentrations by 25%. Trials conducted for testing drug interactions with anti-retrovirals demonstrated the lack of clinically significant drug-drug interactions with Tenofovir, Efavirenz, Lopinavir, and Ritonavir.[18]

Delamanid Resistance

Resistance to Delamanid has been thought to be associated with mutations in mycobacterial F420 genes (Rv3547, fgd, fbiA, fbiB, fbiC) which are linked to

Table 1: Current status of delamanid approval[9,29]

Country	Year	Status
European Union (EU)	2014	Approved
Japan	2014	Approved
South Korea	2014	Approved
India	Aug, 2017	Approved

the activation of the prodrug. A cut off of 0.2 microg/ml was used to delineate mycobacterial resistance in clinical studies however this needs more validation.[8] The frequency of Delamanid resistance *in vitro* is comparable to isoniazid, ranging from $1/10^6$ to $1/10^5$ organisms.[19] *In vivo* resistance could be observed in patients treated with few or ineffective anti-TB drugs.[8,20] Hence, appropriate companion drugs should be used when Delamanid is administered.[19] Although it acts by inhibition of cell wall synthesis, Delamanid does not exhibit cross resistance to Isoniazid.[8] It also does not exhibit cross-resistance to rifampicin, ethambutol, or streptomycin as well as no antagonistic activity to these drugs.[8]

Delamanid in Children

MDR TB as well as XDR TB is often harder to diagnose in children due to lower number of bacilli present in the sputum. Hence, there is limited reporting and diagnosis of TB in children. There is evidence of a case report where Delamanid was used for a case of XDR TB in Italy on compassionate use basis. Delamanid is being studied in paediatric population and trials are going on in several countries.[16] However, according to WHO recommendations given in 2016, Delamanid can be added to the longer regimen in children and adolescents with MDR/RR TB who are not eligible for shorter regimen. (conditional recommendation).[21] A recent systematic review revealed that Delamanid in children seems to be promising, and was well tolerated and effective, as 13 out of 16 children undergoing treatment for more than a few days achieved smear and culture conversion. However, no information is currently available on the combined use of Delamanid and Bedaquiline in children.[22]

Delamanid in Pregnancy

There is limited data regarding use of Delamanid in pregnant women. Animal studies have shown reproductive toxicity. It is not recommended for use in pregnant women or women of child bearing potential in the absence of reliable form of contraception.[15]

Delamanid in TB with HIV

Clinical trials are ongoing with respect to use of Delamanid in HIV patients. Some trials have shown lack of drug interactions with anti-retroviral drugs which is an important aspect favouring its introduction in treatment regimens for HIV co-infected subjects.[18] As per the interim policy guidance released by WHO, the current recommendation for the use of Delamanid applies to adults (≥18yrs) with pulmonary MDR-TB disease, including people living with HIV.[17] However, due to lack of published evidence so far on the use of Delamanid in HIV-infected MDRTB patients on Anti-Retroviral Treatment (ART), patients receiving Delamanid as part of MDR-TB treatment should have their ART regimens designed after careful discussion with clinicians and specialists in the respective fields.[17]

Current Status of Delamanid in MDR TB

Table 1 shows that Delamanid first received conditional approval in the EU for use in combination with optimised background therapy.[9] It has been granted Orphan drug status in both EU and Japan.[9] By September 2017, out of 688 patients who received Delamanid from over 40 countries, only 51 were from India. Delamanid has not yet been launched by Otsuka in India. Otsuka licensed Mylan to market the drug in India and South Africa through a conditional access program to enroll 400 patients on delamanid by early 2018 was planned.[23,24]

Delamanid is also currently undergoing phase III trial in seven countries (Estonia, Latvia, Lithuania, Moldova, the Philippines, Peru, South Africa) in patients with pulmonary MDRTB.[25,26] It has not been approved in the United States. The first-ever phase III randomized controlled clinical trial, by the name of '*Trial 213*' for MDR-TB treatment was completed in October 2017. A position statement was released in by the WHO Global Tuberculosis Programme on the use of Delamanid in MDR-TB, following an expedited review of this trials results which were released at the 48th UNION World Conference on Lung Health in Mexico in October 2017. The robust phase II trial with Delamanid 100 mg twice daily for 2 months had demonstrated a significantly higher rate of sputum culture conversion than placebo, which led to its approval.[9] However, Trial 213 did not confirm the efficacy findings from the phase II trials, although the safety conclusions were the same.[26] Table 2 summarizes the ongoing clinical trials for Delamanid.

Médecins Sans Frontières (MSF) has supported national TB programs of several countries and introduced Delamanid for patients at high risk for poor treatment outcomes, in accordance with the World Health Organization recommendations. Out of a total of 53 patients from 7 countries, which were given Delamanid between February 2015 and 2016, 73.6% (39/53) of patients had a favorable response. These results indicate good tolerability and treatment response at 6 months in a difficult-to-treat cohort of patients. Delamanid was preferred to Bedaquiline, in various cohorts such as Hepatitis C patients, due to its less potential hepatic toxicity as well as in patients taking antiretroviral drugs due to its fewer drug interactions.[27]

Recommendations Regarding Delamanid use

Despite the treatment of MDR TB gaining focus and advances in treatment modalities, a meta-analysis conducted by Kibret et al showed a low treatment success rate and failure to achieve the WHO target set for 2015. It was observed that 14% patients defaulted from treatment whereas 12.6% died, showing that the management of MDR TB is far from satisfactory.[23]

According to WHO, Delamanid should be retained in country guidelines, national essential medicine lists and the addition of Delamanid should be considered when an MDR-TB regimen with four effective drugs, consisting of a Fluoroquinolone (FQ) and an injectable agent in addition to Pyrazinamide, cannot be designed (additional resistance to FQ or an injectable agent, drug intolerance or contraindication). It may also be added for patients at higher risk of poor outcomes.[26,28] WHO has laid down the following conditions for Delamanid

Table 2: Ongoing Clinical Studies on Delamanid[30]

Title	Condition and interventions	Phase	Status
A 6-Month Safety, Efficacy, and PK Trial of Delamanid in Pediatric Patients with Multidrug Resistant Tuberculosis	MDR TB; Pediatric Delamanid Doses – 5,10,25,50,100 mg (age based doses)	II	Recruiting
Evaluating the Pharmacokinetics, Safety, and Tolerability of Delamanid in Combination With Optimized Multidrug Background Regimen (OBR) for Multidrug-Resistant Tuberculosis (MDR-TB) in HIV-Infected and HIV-Uninfected Children With MDR-TB	TB; HIV Infections Delamanid (Dose based on age and weight)	I/II	India - Not yet recruiting Globally – Recruiting
Treatment Shortening of MDR-TB Using Existing and New Drugs	TB; MDR TB Linezolid, Delamanid, Pyrazinamide, Levofloxacin,	II	Recruiting
Evaluating Newly Approved Drugs for Multidrug-resistant TB	TB; MDR Bedaquiline; Delamanid; Clofazimine; Levofloxacin; Moxifloxacin; Linezolid; Pyrazinamide	III	Recruiting
Evaluating the Safety, Tolerability, and Pharmacokinetics of Bedaquiline and Delamanid, Alone and in Combination, For Drug-Resistant Pulmonary Tuberculosis	TB, HIV Infections Bedaquiline, Delamanid, Dolutegravir	II	Recruiting
Pharmacokinetic Study of Antiretroviral Drugs and Related Drugs During and After Pregnancy	Antiretroviral drugs (ARV) + Anti-TB, ARV, Anti-TB	IV	Recruiting

use[15,26]

i. careful selection of patients that are likely to benefit;
ii. informed consent of the patients;
iii. adherence to WHO recommendations in designing a longer MDR-TB regimen;
iv. close monitoring of clinical treatment response;
v. active TB drug-safety monitoring and management

In India, Delamanid has been approved for the use as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis (MDR-TB) in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability.[29] Delamanid can be a valuable addition to the available treatment options where no other drugs have shown effect.

Conclusion

The World Health Assembly has adopted the WHO End TB Strategy in May 2014 which aims to end the TB epidemic by 2030 and ensure that no family is burdened with catastrophic costs due to TB. It is also among the health targets of the newly adopted Sustainable Development Goals.[31] There are still a number of hurdles in combating the burden of MDR TB which include timely detection of cases, providing quality assured treatment which is of a relatively shorter duration, cost effective and associated with minimal side effects in order to assure maximum compliance. Incorporation and judicial use of Delamanid in regimen of MDR TB is an important step in this direction.[31] There will be more data available in near future to confirm role of Delamanid treatment regimens in paediatric population, HIV co-infection and regarding combined use with Bedaquiline. Data from observational studies following its use in limited access programmes will also add to the evidence.

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