Educational Forum

Delamanid and its role in drug-resistant tuberculosis

Das S[1], Sehgal VK[2]

[1]Dr Supratik Das
Post Graduate Student
[2]Dr Vijay Kumar Sehgal
Associate Professor
vijayksehgal@yahoo.com
[1,2]Department of Pharmacology
Govt. Medical College, Patiala
Punjab, India

Received: 23-09-2016
Revised: 22-10-2016
Accepted: 28-11-2016

Correspondence to:
Dr Supratik Das
suprateek123@yahoo.co.in

ABSTRACT

The World Health Organisation estimates that one-third of the world's population are currently infected with Tuberculosis bacillus, 10% of whom will develop the disease at some point in their lifetime. Poverty-Stricken countries of Africa and Asia bear the brunt of the disease partly due to an ominous synergy between mycobacterium bacteria and HIV. The recent recognition of MDR-TB and strains with more complex resistance patterns has stimulated the development of new TB medications including fluoroquinolones, oxazolidinones, diarylquinolines, nitroimidazopyrans. 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. The purpoe of this article is to bring forward, the various roles played by Delamanid in order to curb the problem of Multi-drug resistant Tuberculosis.

Keywords: *Delamanid, nitro-dihydro-imidozooxazole, pro-drug, multidrug-resistant tuberculosis, mycolic acid inhibitor*

Introduction

Tuberculosis (TB) is caused by infection with Mycobacterium Tuberculosis, which is a part of a complex of organisms including M. bovis and M. africanum. It's bacilli is spread by the inhalation of aerosolised droplet nuclei from other infected patients. Once inhaled, the organisms remain in the alveoli and initiate the invasion of macrophages and lymphocytes. Mycobacterium tuberculosis bacilli can survive inside macrophages after phagocytosis, unless these cells are activated by cytokines produced by T-Helper cells.[1] Between 2010 and 2011, the incidence of TB decreased to 2.2%. Since 1990, TB mortality declined to 41% and the 2015 millennium development goal of reducing the 1990 TB mortality rate by 50% will likely be achieved.[2] The resurgence of TB has largely driven in Africa and former Soviet Union and Baltic states by lack of appropriate health care along with social and political upheaval[3] and the prevalence of Multidrug-resistant Tubeculosis is rising, particularly in Asia, Africa.[4] Multidrug-resistant tuberculosis (MDR-TB) is the development of resistance to rifampicin and isoniazid. 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).[3] Combination of 2 or more drugs are required to overcome these obstacles and to prevent emergence of resistance during the course of therapy.[5] 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. Newer targets and drugs against TB are being explored out of which, a new drug Delamanid received conditional approval by European Medicines Agency (EMA) for the treatment of MDR-TB in November 2013.[3]

Delamanid is a novel drug which is expected to help in curbing the menace of Multi-drug resistant Tuberculosis. Even though, other drugs are there, they are not showing to be fully effective against it. Thus, the purpose of this article is to shed light on this novel drug regarding its role in this situation, and to spread the

message that yes, this menace of Multi-drug resistant Tuberculosis can still be won.

Drugs used to treat tuberculosis

For centuries, tuberculosis was a major killer disease, but the introduction of **streptomycin** in the late 1940s followed by **isoniazid** and, in the 1960s, of **rifampicin** and **ethambutol** revolutionised therapy, and tuberculosis came to be regarded as an easily treatable condition.[1]

Tradiionally, the drugs used to treat tuberculosis are placed as:

First line essential drugs[6]

Isoniazid (INH), Rifampicin, Pyrazinamide and Ethambutol are fist line, most effective and are the basic components of the antitubercular treatment.

First line supplemental drugs[6]

Rifabutin, Rifapentin and Streptomycin are first line supplemental drugs. Streptomycin is a reserved drug and is used for special settings. They possess an acceptable limit of toxicity.

Second-line drugs include[6]

- Fluoroquinolones
- Amikacin
- Capreomycin
- Ethionamide
- Para-aminosalicyalic acid
- Cycloserine
- Thiacetazone

These drugs are used in case of resistance against first-line drugs or due to their contraindication.

Drugs for multi-drug resistant tuberculosis

Emergence of Multi-Drug Resistant Tuberculosis (MDR-TB) have obstructed efforts for successful prevention and treatment of TB. Presence of AIDS/Diabetes further complicates this problem. Patients of MDR-TB have to undergo lengthy courses of treatment, they are subjected to severe side effects. moreover treatment regarding this is expensive, along with poor success rates. However, the most commonly used regimen used for MDR-TB is:

- **For Isoniazid (INH) resistance:**
  Rifampicin (RMP) + Pyrazinamide (PZA) + Ethambutol (ETB) for 12 months
- **For Rifampicin (RMP) resistance:**
  Isoniazid (INH) + Pyrazinamide (PZA) + Ethambutol (ETB) for 12 months
- **For both Isoniazid (INH) and Rifampicin (RMP) resistance:**
  Pyrazinamide (PZA) + Ethambutol (ETB) + Streptomycin (SM)/ Ethionamide + Ciprofloxacin/Ofloxacin/Levofloxacin, for 12-18 months

Need for delamanid

New tuberculosis (TB) drug regimens that shorten and simplify the current treatment are now needed for all patient populations. An ideal new TB drug would be well tolerated, be orally dosed once daily, and have a low cost. It would demonstrate bactericidal and sterilizing efficacy and have a novel mode of action and therefore show utility against both drug-sensitive and drug resistant TB. Current treatment regimens for multi-drug resistant tuberculosis (MDR-TB) are associated with low treatment success rates, are toxic, and require long duration of treatment. Thus, need for shorter and more effective treatment regimens is urgent.[7,8,9] After a gap of nearly 50 years, new classes of tuberculosis antibiotics are under development.[2] Delamanid, previously named OPC-67683, a Nitro-dihydro-imidazo-oxazole, is undergoing commercial development.[2,8,9] It is a new agent which prevents mycolic acid synthesis, has shown potent in vitro and in vivo activity against both drug-susceptible and drug-resistant strains of M. tuberculosis in preclinical development.[10]

A Phase IIb randomised controlled trial in adults with pulmonary MDR-TB, showed improved rates of sputum culture conversion at 2 months when an OBR was augmented with delamanid as compared to placebo . An open-label extension of this trial found that patients who consumed Delamanid for 2–6 months had more positive outcomes (cured or completed treatment) and lower mortality than those who took delamanid for ≤2 months.[9]

It has been included in the World Health Organization (WHO) Model List of Essential Medicine by the WHO Expert Committee on Selection and Use of Essential Medicines.[7]

Japanese researchers who are investigating the properties of the nitro-dihydro-imidazooxazoles, found that Delamanid had superior activity against MTB than other closely related compounds.[2] While this drug has been included in international guidance for the treatment of MDR-TB since April 2014, access, particularly in countries with the greatest need, has been challenging. By end of December 2014, less than ten patients outside clinical settings had received Delamanid. Recently, at the WHO Global Laboratory Initiative Partners Forum in Geneva; heralded as the "FightBack Initiative" Otsuka (the drug's developer) announced.[7] It is hoped that these new drugs will improve the treatment of drug-resistant forms of TB, in terms of both better outcomes and quality of life for patients.[11]

Mechanism of action

Delamanid is a Dihydro-nitroimidazooxazole derivative. It is a pro-drug which gets activated by the enzyme deazaflavin dependent nitroreductase (Rv3547). A reactive intermediate metabolite,is formed between delamanid and desnitro-imidazooxazole derivative.[3,12] It acts by inhibiting the synthesis of mycobacterial cell wall components, methoxy mycolic acid and ketomycolic acid.[3] Mycolic acids are long chain fatty acids that show hydrophobicity to the mycobacterial cell wall by impeding drug penetration into mycobacteria.[2] Its activity also requires the mycobacterial deazaflavin F420-dependent glucose-6-phosphate dehydrogenase (G6PD), Fgd 1.[2] The inhibitory concentrations of delamanid (IC50) for methoxy- and ketomycolic-acid biosynthesis are 0.036 mcg/mL and 0.021 mcg/mL,are respectively less than Isoniazid. Unlike Isoniazid, Delamanid does not inhibit α-mycolic acid synthesis. Despite the absence of an effect on α-mycolic acid synthesis, the MICs reported with delamanid are 2 to 32 times less than Isoniazid.[2] Resistance to Delamanid is by mutations of either F420 or Fgd 1. Mutations of Rv3547, the gene coding for the deazaflavin-dependent nitroreductase, also produce mycobacterial resistance to Delamanid. Nitroimidazoles also appear to kill TB bacteria by poisoning them with nitric oxide, which the drugs release when metabolized. Therefore, according to its registered indication, this designated, "orphan drug" may be used to treat "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.[7,12]

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. Steadystate 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.[3] Delamanid has minimal effects on CYP in concentrations up to 100 μM since it is not metabolized by the cytochrome P450 enzymes (CYP). Therefore, interactions with other drugs should not be a problem. In patients co-infected with HIV, the lack of interaction with ART is a major advantage. Delamanid can be administered with rifampin without either drug affecting the metabolism of the other. This is an important advantage over Bedaquiline which is metabolized by CYP. Caution is required in patients receiving other medications that also cause QT prolongation or hypokalemia.[2]

Adverse effects

- The incidence of QT Prolongation (most serious adverse effect[1]) was observed to be frequent 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.[3]
  - Nausea, vomiting and dizziness (In about 1/3rd of people taking it)[8]
  - Low potassium levels in the blood.[8]

- Paresthesia (a pricking or tingling sensation), anxiety and tremor.[8]

Dosing/ contraindications

Delamanid (Deltyba) is made in 50 mg oral tablets. The recommended dose is 100 mg twice daily, given for 6 months (24 weeks), as part of an MDR-TB treatment regimen.[7] Serum albumin is believed to be the primary route of metabolism with minimal involvement of hepatic cytochromes. Co-administration with food (specially fatty meals) has been shown to have a significant impact on drug absorption and it is recommended that delamanid be given with food. Hypoalbuminemia has been associated with an increased risk of QTc prolongation. Therefore, delamanid is contraindicated in patients with albumin level of, 2.8 g/dL. Co-administration with strong CYP3A inhibitors (eg, lopinavir/ritonavir) and fluoroquinolones may also lead to QTc prolongation and frequent monitoring of electrocardiograms throughout the treatment period is recommended when co-administration with these drug classes is required.[7]

Clinical trials[3]

Early bactericidal activity: 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.

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

Long-term trial: There was significant reduction in mortality in the long-term delamanid treated group.

Advantages

High potent action, least chance of drug-drug interactions, better toxicity profile, and post antibiotic effect against intracellular bacilli are advantages of delamanid which will be helpful in reducing the treatment time and risk of toxicity in MDR-TB.[3]

Conclusion

Approval of delamanid has boosted our confidence in managing drug-resistant TB. An important advantage over other medications is that it is not metabolized by CYP enzymes and can be given in combination with ART, rifampin, or with other drugs metabolized by CYP enzymes. QT prolongation is the most concerning adverse effect and could potentially limit its use in patients with co-morbid heart disease. Each and every drug whether new or old has some or other adverse effects, but that should not deter us from our goal regarding tackling a particular disease. It is hoped that in the near future, newer drugs like Delamanid will prove to be an effective weapon against MDR-TB, providing positive results along with an improved safety agenda, an affordable cost and easy availability for the patients. Thus, we can say that an extensive goal oriented scientific research along with a positive attitude can help us achieve new hopes, and heights regarding service of mankind.

References

1. Rang HP, Dale MM, Ritter JM, Flower RJ, Henderson G. Rang and Dale's Pharmacology. 7th ed. Livingstone: Churchill Elsevier; 2012.p.634.
2. Field SK. Safety and efficacy of Delamanid in the treatment of Multidrug resistant Tuberculosis. Clin Med Insights: Therapeutics 2013;5:137-49.
3. Xavier AS, Lakshmanan M. Delamanid: A new armor in combating drug resistant tuberculosis. Journal of Pharmacology and Pharmacotherpeutics 2014;Jul-Sept;5(3): 222-4.
4. Reid PT, Innes JA. Infection of the Respiratory system. Colledge NR, Walker BR, Ralston SH, editors. Davidson's Principles and Practice of Medicine. 21st ed. Livingstone: Churchill Elsevier; 2010.p.688.
5. Deck DH, Winston LG. Antimycobacterial Drugs. Katzung BG, Masters SB, Trevor AJ, editors. Basic and Clinical Pharmacology. 12th ed. New Delhi: Mc Graw Hill Education; 2012.p.839.

6. Sharma HL, Sharma KK. Principles of Pharmacology. 2nd ed. Hyderabad: Paras Medical Publisher; 2013.p.753.
7. Rustomjee R, Zumla A. Delamanid expanded access novel treatment of drug resistant tuberculosis. Dove Press journal: Infection and Drug Resistance 2015 Oct; 8:359-66.
8. Lessem E. An Activist's Guide to Delamanid (Deltyba). Treatment Action Group 2014 Sept:1-6.
9. Sloan DJ, Lewis JM. Management of multidrug-resistant TB: novel treatments and their expansion to low resource settings. Trans R Soc Trop Med Hyg 2016;110:163–72.
10. Gler MT, Skripconoka V, Garavito ES, Xiao H, Rivero JLC, Vasquez DEV, et al. Delamanid for Multidrug-Resistant Pulmonary Tuberculosis. N Engl J Med 2012 June;366(23):2151-60.
11. Brigden G, Hewison C, Varaine F. New developments in the treatment of drug-resistant tuberculosis: clinical utility of bedaquiline and delamanid. Dove Press journal: Infection and Drug Resistance 2015 Oct;8:367-78.
12. Upton AM, Cho S, Yang TJ, Kim Y, Wang Y, Lu Y, et al. In Vitro and In Vivo Activities of the Nitroimidazole TBA-354 against Mycobacterium tuberculosis. Antimicrobial Agents and Chemotherapy 2015 Jan;59(1):136-44.

Cite this article as: Das S, Sehgal VK. Delamanid and its role in drug-resistant tuberculosis. Int J Med and Dent Sci 2017; 6(1):1449-1453.

Source of Support: Nil
Conflict of Interest: No