Progress of Delamanid in the Treatment of Tuberculosis

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Abstract: Tuberculosis has been a prevailing disease across the globe, threatening millions of people's lives. With the mutation in mycobacterial cells, the number of drug-resistant tuberculosis bacteria and widely drug-resistant tuberculosis bacteria is increasing rapidly. The first line drugs such as Ethambutol, Rifampicin, and Pyrazinamide fail to control the spread of those tuberculosis, stressing the demand for new treatment to combat the infectious disease. Delamanid, a recently approved drug by the FDA, gives hope in tackling the surging number of Tuberculosis disease. Delamanid is effective in destabilizing the mycobacterial cell wall, thus can enter and destroy the bacteria. Clinical trials in China, South Korea, and Latvia all show positive results - Delamanid is effective and safe. Its positive clinical trials show the drug's promising effect. However, possible side effects such as causing heart rhythm problems and the lack of human clinical trials should be taken into consideration, especially when implementing delamanid in Tuberculosis treatments. By assembling and analyzing the current research on Delamid and its effects on the disease, we review the current problems of tuberculosis human beings face, delamanid as the possible solution, its mechanism and effectiveness of addressing the disease. In total, Delamanid is proven to be a promising regimen of tuberculosis and can be broadly applied with more reassuring clinical trials.

1. Introduction

Mycobacterium tuberculosis, being a popular bacterium in nature, is passed on through respiratory tract, alimentary tract, and injured skin. In the past, eliminating and/or controlling the infected cases were the main roadmaps to end the TB. Tuberculosis was under control in the last century with the living standard going up and the introduction of the Bacillus Calmette-Guerin (BCG) vaccine. BCG is given to infants and young kids in other countries where TB is common but not widely used in the US, which can help infants and small children getting resistance to severe pulmonary Tuberculosis. BCG, however, provides weak protective effects on adults and thus the occurrence of Tuberculosis cannot be stopped. The incidence of tuberculosis has become higher again since the 1990s' due to the emergence of HIV, immunosuppressant drugs, population migration, which prompt low immunity and higher risk of contagion among people. TB, being the world's most deadly infectious disease, takes over 1.5 million lives a year. In 2019, there were about 9.96 million newly confirmed cases of TB, of which men (aged ≥15 years) accounted for 56%, women accounted for 32%, and children (aged <15 years) accounted for 12%. Among all of those affected, 8.2% were people living with HIV [1]. Worse, the increase of multidrug-resistant tuberculosis (MDR-TB, resistant to first-line anti-TB medications) and extensively drug resistant tuberculosis (XDR-TB, resistant to second-line medications) add on to the difficulty the world faces. The effective 6-month combination treatment for TB using four first-line drugs (rifampicin, isoniazid, pyrazinamide, and ethambutol) has been available since the 1980s [1]. These regimens, however, don't work well for either MDR-TB or XDR-TB. If the

demand for new treatment can't be fulfilled soon, those infected with MDR/RR-TB will continue to be the source of TB and threaten public health as TB is spread by coughing and sneezing.

Delamanid (molecular formula C25H25F3N4O6), a nitro-dihydro-imidazo oxazine derivative, is a new anti-MDR TB medication developed recently. Delamanid inhibits the synthesis of methoxy-mycolic and keto-mycolic acid, which are constituents of the mycobacterial cell wall; the drug does not inhibit alpha-mycolic acid, unlike isoniazid [2-3]. Delamanid works by blocking the manufacture of mycolic acids thus destabilizing the bacterial cell wall and destructing the mycobacteria.

Delamanid brings light to those of MDR-TB. Its Phase I, II, III trial results are promising. The World Health Organization (WHO) guidelines suggested that there are no additional safety concerns for concurrent use of delamanid with bedaquiline [4]. To those of unfavorable prognosis or M/XDR-TB, delamanid can work as an effective ancillary drug. Despite all of these, the WHO still classified delamanid as a group C drug as there are concerns on its side effects, such as an increase in the QT interval which can cause heart rhythm problems. Although no high incidence of adverse effects was reported, the limited human being trial data does not support the safety of the drug. Further investigations are necessary to study the safety and efficiency of delamanid in the pediatric population. This paper will provide an overview of Tuberculosis, introduce the newly approved drug Delamid and its mechanism, and analyze its recent clinical trials.

2. The incidence of Tuberculosis

Approximately 5-10% of the individuals infected with Mycobacterium tuberculosis develop the disease during the first 2-5 years after infection [5]. Figure 1 gives the death rate by age per 100,000 people from 1990 to 2017, over 50% drop on the death rate achieved in the last 30 years because of living standards, medical treatment improvement, test method upgrade, and vaccine implementation in the group of children. In 2017, the death rate of people above 70 years old is 71.91, and those aged 15 to 49 is 9.5 per 100,000 population.

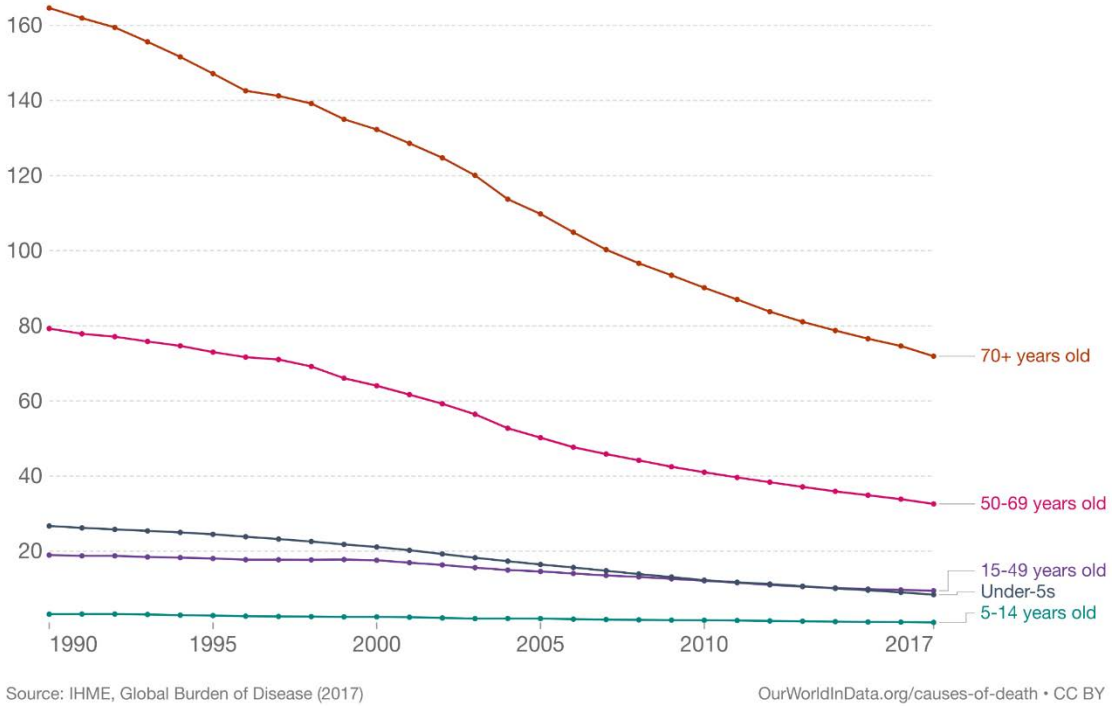

Figure 1. Death rate from tuberculosis by age, World, 1990 to 2017 [6]. The annual number of deaths from tuberculosis per 100,000.

In 2018, 1.7 billion people were infected with tuberculosis (TB), which is roughly 23% of the world's population [7]. In 2019, there were around 9.96 million new cases of TB. Among all of those affected, 8.2% were people living with HIV [1] who have compromised immune problems. This made the global average incidence rate of TB about 130 per 100,000 population per year. It was the 13th

leading cause of death worldwide and the top cause from a single infectious agent that year [1]. In 2020, TB took over 1.5 million lives including 214,000 people with HIV [8].

The resistance of TB bacteria to many drugs is due to genetic changes in the bacteria. The mechanism of MDR-TB comes from but not limited to 1) complex lipid molecules in the cell wall of M. tuberculosis function as a barrier to prevent the drugs from getting into the cell; 2) The drug molecules are neutralized or forced out by the TB cell molecule system; 3) Spontaneous mutations in the TB genome can alter proteins which are the target of drugs, making the bacteria drug resistant [9], etc.

Worldwide in 2019, rifampicin-resistant TB (RR-TB) was developed in close to half a million people. Among those, 78% had MDR-TB. Meanwhile, 3.3% of the new TB cases and 17.7% of previously treated cases turned into MDR/RR-TB [1]. The treatment success rate of MDR-TB was 52%, and death rate was 17%. While XRD-TB, harder to treat and more deadly, has a treatment success rate of only 28% and a death rate of 27% [10].

3. Treatments for Tuberculosis and Multidrug-resistant Tuberculosis

Mycobacterium tuberculosis cell wall is characterized by a complex structure, composed of inner and outer layers. The outer layer contains lipids and proteins. The inner layer is composed of peptidoglycan, arabinogalactan, mycolic acid which is covalently linked to form a complex structure that extends from the plasma membrane in the outer layer to mycolic acid [11]. Mycolic acid, a long chain fatty acid, covalently bound to arabinogalactan peptidoglycan copolymer [12]. Peptidoglycan forms the backbone of the cell wall.

The first breakthrough in TB therapy was the discovery of the tubercle bacillus by Robert Koch in 1882. The main disadvantage of this treatment is its long duration, which takes 6 to 9 months. This effective 6-month combination treatment for TB is recommended by WHO. It has been available since the 1980s and uses four first-line drugs (rifampicin, isoniazid, pyrazinamide, and ethambutol) [1].

Ethambutol (EMB), one of the first line drugs, was developed in the 1960s, which was much more tolerated than the combination of adding is nicotinic acid hydrazide (INH) to para-amino salt (PAS) and streptomycin (SM). Meanwhile, EMB is capable of reducing the TB treatment from 2 years to 1.5 years while maintaining the cure rate at 90-95% [13]. The next major development in TB therapy was the introduction of rifampicin (RIF). If it is used with INH, SM, EMB, it could result in >95% cure rate within 8-9 months. It not only has a higher cure rate; it also significantly reduces the treatment duration. The outstanding performance of RIF is attributed to its capacity to kill mycobacteria undergoing sporadic metabolism [14]. The treatment length is reduced to 6 months while keeping the >95% cure rates when Pyrazinamide (PZA) is implemented with INH and RIF [15]. It has been speculated that the amazing effect of PZA is caused by its activity against tubercle bacilli in the acidic debris in pulmonary cavity walls [15]. This is consistent with the observation that PZA exerts all of its beneficial effects in the first 2 months of therapy [14]. The combination therapy was efficient in the past. Unfortunately, it is not so effective in dealing with the MDR-TB and XDR-TB.

4. The mechanism of Delamanid in the treatment of Tuberculosis

Dramani is a drug of the bicyclic nitroimidazole class. The bicyclic nitroimidazoxazole (2-nitroimidazole) is an analogue of azithromycin, which has strong pharmacological activity against tuberculosis. The 2-substituent of 6-nitro-2, 3-dihydroimidazole [2,1-b] oxazole accelerates the anti-tuberculous activity and reduces the mutagenicity, which is a mixture with a racemic structure. Therefore, the right-handed enantiomer has the activity of an anti-mycobacterium tuberculosis complex (MTBC). Delamanid is a compound with a relatively safe range of drug concentration and only has a good effect in vivo and in vitro [16].

The molecular formula of Delamanid is C25H25F3N4O6. Its type is small molecule with an average of 534.492 and isotope 534.17261903. The World Health Organization considers it a solid oral treatment for tuberculosis. Delamanid is an antimycobacterial derived from nitro-dihydro-

imidazooxazole compounds that inhibit mycolic acid synthesis in bacterial cell walls. It has anti-mycobacterium activity. After oral administration, the prodrug Delamanid is activated by the mycobacterium F420 coenzyme system to form reactive intermediate metabolites that inhibit the synthesis of mycobacterium cell wall components methoxy-mycobacterium and keto-mycobacterium acid. This leads to depletion of these cell wall components and destruction by mycobacteria. The minimum inhibitory concentration (MIC) of Delamanid against M. tuberculosis was 0.006-0.024 g/mL. Among non-tuberculous mycobacteria, Delamanid has in vitro activity against mycobacterium tuberculosis. Delamanid is a precursor drug that requires biotransformation through the Mycobacterium F420 coenzyme system. It includes a deazaflavin-dependent nitro reductase (Rv3547) to regulate its antibacterial activity against growing and non-growing mycobacteria. Mutations in one of the five coenzyme genes of F420, FGD, Rv3547, fbiA, fbiB and fbiC, are thought to be the mechanism of Delamanid resistance. Activation of F420 by F420-dependent nitro reductase encoded by ddn gene can transform the dicyclic nitroimidazole drug into an intermediate metabolite and a denitrogenated form of Delamanid. The FbiA gene encodes a protein, which essentially acts as a transferase and can catalyze the conversion of phosphoenolpyruvate to F420-o. At the same time, FbiB can encode a γ-glutamyl ligase, which participates in the dehydrogenation reaction and dehydrogenates F420-0 to F420-0. FbiC participates in the steps of F420-0 synthesis and encodes a synthase that facilitates the entire process. Recent studies have shown that FbiD, as a cofactor, also participates in the biosynthesis of F420, and plays an important role in the synthesis pathway by carrying out the phosphate group FbiA in the subsequent steps. Finally, the fgd1 gene encoding G6PD protease plays a key role in the synthesis of F420. Participate in the redox cycle reaction, which mainly oxidizes 6-phosphoglucose to 6-phosphogluconolactone. Upon activation, free radical intermediates formed between Delamanid and desnitro-imidazooxazole derivatives are thought to mediate the action of antifungal bacteria by inhibiting the synthesis of methoxy-mycolic and keto-mycolic acids. This results in depletion of mycobacterium cell wall components and destruction of mycobacterium [16].

After catalyzing the metabolites formed by the partial cleavage of 6-nitro-2,3-dihydroimidazole-[2,1-b] oxazole, DLM continues its metabolism. The hydroxylation of the oxazole part changes, which is the starting point of M2. But this process is very short, the reaction will continue to occur and continue to be oxidized to the ketone form (M3). This metabolic process is mainly performed by CYP3A4. For anti-tuberculosis drugs, the PK variability between individuals is very large because of the many ways and mechanisms of drug-drug interactions. Including the induction or inhibition of metabolism and drug transport of P-glycoprotein by the enzyme hepatocellular pigment P450 [17].

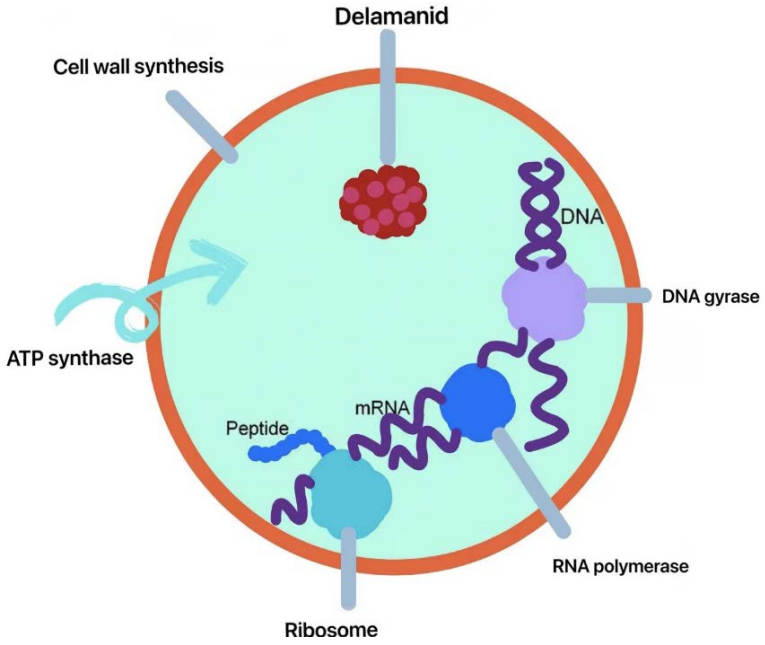

Figure 2. Antituberculous drug (Delamanid)- site.

5. The Clinical trials of Delamanid

Otsuka Pharmaceutical Development and Commercialization Company conducted related experiments. The trial compared the use of Delamanid plus OBR treatment (experimental group) with placebo plus OBR treatment (control group). In this trial, a total of 511 participants were randomly assigned to receive study medication (IMP) and optimized background therapy (OBR) for 6 months, and they received OBR alone for 12-18 months. In addition, the trial also includes a follow-up period of 6-12 months after treatment. The results showed that the experimental group was 6 days less than the control group. And in the second month, the sixth month and the 30th month, the experimental group and the control group had 58%, 87.6%, 76.5% and 53.5%, 86.1% and 77.2%, respectively. From the results of this experiment, it can be seen that the use of Delamanid can reach SCC earlier than placebo, indicating that it is indeed effective in the treatment of multidrug-resistant tuberculosis [18].

In addition, in a trial of pediatric patients with multidrug-resistant tuberculosis (MDR-TB), 37 participants were divided into four groups based on age. Participants aged 12 to 17 received oral Delamanid 100 mg plus OBR daily until day 182, and continued OBR treatment until day 365. Participants from 6 to 11 years old received the oral adult preparation Delamanid 50 mg treatment (BID) plus OBR until day 182, and then continued to receive OBR until day 365. Participants aged 3 to 5 received oral 25 mg Delamanid (DPF suspension prepared using dispersible tablets), pediatric preparation (BID) and OBR treatment until day 182, and continued OBR treatment until day 365. Participants from birth to 2 years of age received 182 days of DPF (suspension prepared with dispersible tablets) plus OBR treatment, and then continued to receive OBR treatment until day 365. The test showed that the proportion of participants with good treatment results (cured or completed) in the first group of the trial was 85.7%, and the second group had good treatment results. The proportion of subjects in the third group was 100%, the proportion of subjects with good treatment effects in the third group was 83.3%, and the proportion of subjects with good treatment effects in the fourth group was 91.7%. Judging from this result, Delamanid does have a significant effect in the treatment of multidrug-resistant tuberculosis, and the treatment success rate is also relatively high [19].

In a follow-up evaluation, the researchers conducted a 24-month observational follow-up of 481 (87.5%) patients from the original randomized controlled trial. This analysis proved the follow-up effect of Delamanid combined with OBR on the treatment outcome of MDR-TB patients. It was found through observation that among 192 patients who received Delamanid treatment for at least 6 months, 143 (74.5%) got good results. Of the 229 patients who received Delamanid treatment for less than 2 months, 126 (55%) had good results. In addition, only 2 deaths (1.0%) occurred in the long-term treatment group, while 19 deaths (8.3%) occurred in the short-term treatment group. Compared with patients who received short-term or no Delamanid, the researchers found that the mortality of patients who received long-term Delamanid treatment was reduced to 1.0% (8.3%; $p<0.001$). The results of the trial showed that the use of Delamanid for 6 months and prolonged treatment in patients with multidrug-resistant and extensively drug-resistant tuberculosis can reduce the mortality of patients [20].

In a Chinese clinical trial for the treatment of patients with multidrug-resistant tuberculosis, a total of 38 patients participated in the trial. Among them, 26 patients used Delamanid's regimen (treatment group) and 12 received placebo (control group). They received treatment for 56 days. The results of the test showed that 24 patients (92.3%) in the treatment group and 11 patients (91.7%) in the control group had tooth decay. Thirty-two pulmonary tuberculosis cases (median 74.5 days) were cultured. Thirty patients successfully completed treatment before the end of treatment and were recorded as negative cultures. There are two patients who have been negative for 5 consecutive cultures and are still receiving treatment. Six of these patients had poor results. In 13 patients, adverse events observed in the trial included mental disorders, prolonged QT interval, and elevated blood cortisol, while only three patients discontinued Delamanid treatment due to adverse events. After analyzing this trial, the conclusions reached show that Delamanid is well tolerated, has a low rate of discontinuation, and can effectively treat multidrug-resistant tuberculosis [21].

In a study in South Korea, data showed that the Delamanid-containing program achieved a 95% culture conversion rate within 6 months. A total of 49 patients were treated with Delamanid during the study period. Among these 49 patients, 40 cases (81.6%) were successfully treated. Thirty patients underwent a median follow-up of 201 days (IQR 103.5-311.5 days) after the end of treatment, and the data showed that there was no recurrence. Nine patients (18.4%) had unfavorable results. Three patients died during treatment. Because these patients were culture-negative at the time of death, the researchers believe that Delamanid is unlikely to be related to all deaths. Treatment failures occurred in three patients, one was lost to follow-up, and two were not evaluated. This study shows that a regimen containing Delamanid can achieve a high treatment success rate in dealing with difficult-to-treat MDR-/XDR-TB patients [22].

In a trial of patients with multidrug-resistant and extensively drug-resistant tuberculosis treated with Delamanid in Latvia, a total of 19 patients received final treatment results. The test showed that all patients had lung diseases, and two patients (10.5%) had other extrapulmonary diseases besides lung diseases. Among them, 13 patients (68.4%) had received treatment for tuberculosis. 2 patients (10.5%) had MDR-TB, 8 patients (42.1%) had XDR-TB, and 9 patients (47.4%) had XDR-TB. One patient (5.3%) was HIV positive. The average duration of treatment for patients with Delamanid was 31.2 weeks. In the trial, 16 patients (84.2%) received Delamanid treatment for at least 24 weeks. Three patients (15.8%) received Delamanid treatment for less than 24 weeks. However, the final treatment results showed that 16 cases (84.2%) were cured and completed the treatment without failure. At the same time, at least 3 consecutive times after the intensive period were culture-negative at intervals of at least 30 days, and 3 patients (15.8%) were lost to follow-up, and there were no deaths or treatment failures. The overall duration of MDR-TB treatment in 16 cured patients ranged from 11 to 19 months (average 15 months). None of the 19 patients in this trial experienced recurrence. This study supports the effectiveness and safety of Delamanid in the treatment of MDR-TB and reflects its beneficial results in the treatment of MDR-TB patients in Latvia's national pulmonary treatment program [23].

6. Conclusion

Tuberculosis is worth the public attention, especially with the emergence of MDR-TB and XDR-TB which are impossible to cure. Luckily, Delamanid, a new antituberculosis medication, is developed as an effort to defeat MDR/XDR-TB. The placebo-controlled trial proves the effectiveness of Delamanid. The safety and effectiveness of Delamanid are future assured in testing different age group patients, and in different countries (China, South Korea, and Latvia). All of the clinical trials have a cure rate above 50%. Most of the cure rates are between 80% to 90%, with one even reaching 100%. There were unsuccessful cases and deaths, but the incidence rate is very low. From these clinical trials, we can conclude that Delamanid is surely a potential drug to combat the MDR-TB and XDR-TB. However, more human clinical trials on larger scales are needed before the drug officially implements Delamanid in tuberculosis treatments. When possible, side effects and unknown risks are eliminated, Delamanid could be a common anti-TB drug, even becoming one of the first line drugs in the near future. Tuberculosis could again be controlled.

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