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Review

Delamanid In Tuberculosis Management: A Novel Agent Against Drug-Resistant TB

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Abstract

Tuberculosis (TB), primarily caused by Mycobacterium tuberculosis (MTB), continues to pose a significant health challenge worldwide, especially in regions like South-East Asia and Africa. This slow-growing, aerobic bacillus has a unique lipid-rich cell wall that makes it tough and resistant to many drugs. When someone inhales MTB, it targets the lungs and gets taken up by macrophages, which then form granulomas to try to contain the infection. While these granulomas can keep the bacteria dormant, a weakened immune system can trigger a reactivation, leading to active and contagious TB. The rise of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB has made traditional treatments like isoniazid and rifampicin less effective, highlighting the urgent need for new therapies. One promising option is Delamanid, an oral nitro-dihydro-imidazole derivative sold under the name Deltyba, which shows potential against MDR-TB. It works by being activated through the MTB F420 coenzyme system, inhibiting the synthesis of methoxy- and keto-mycolic acids that are essential for the bacteria's cell wall, ultimately leading to their death. Additionally, Delamanid creates oxidative and nitrosative stress through reactive nitrogen species. Clinical trials have shown that combining delamanid with WHO-recommended background treatments can lead to better outcomes and lower mortality rates. However, there is a risk of spontaneous resistance due to mutations in genes related to its activation. While delamanid is generally effective against M. tuberculosis, M. kansasii, and M. bovis, it doesn't show significant activity against other bacterial species. Some side effects, like QTc prolongation, are mainly linked to its metabolite DM-6705. As a new therapy targeting the cell wall, delamanid is a crucial weapon in the fight against MDR-TB, with the potential to reduce transmission, enhance survival rates, and bolster global TB control initiatives.

Keywords: Tuberculosis, *Mycobacterium tuberculosis*, Granuloma, Multidrug-resistant tuberculosis (MDR-TB), Extensively drug-resistant tuberculosis (XDR-TB), Delamanid, Deltyba, Mycolic acid synthesis inhibition, F420 coenzyme, Drug resistance, Antitubercular therapy.

INTRODUCTION

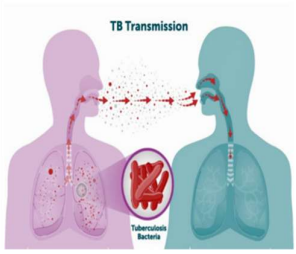
Definition: Tuberculosis (TB), commonly known as "white death" or consumption in the past, is a contagious illness that is usually caused by MTB bacteria [(1)].

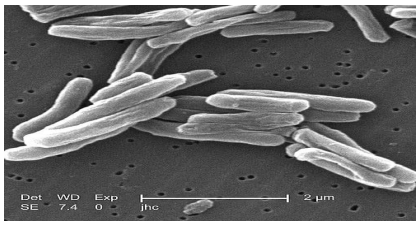
Mycobacteria: TB is primarily caused by MTB, a tiny, aerobic, nonmotile bacillus. Unlike other bacteria, which usually split in less than an hour, it divides every 16 to 20 hours. Due to their complex cell envelope, the high lipid content of the outer membrane serves as an effective barrier that aids in developing drug resistance among Mycobacter.

Fig 1: Transmission of TB **Fig 2: Scanning electron micrograph of M tuberculosis**

Regional Distribution

TB is distributed in different ways:





South-East Asia has the highest burden, with 46% of new cases falling under this category. Although the HIV epidemic is responsible for the highest incidence rates per capita, Africa still experiences 23% of new cases [(2)].

In the Western Pacific, 18% of new cases have occurred. The WHO estimates that the remaining 13% is located in the eastern Mediterranean, Europe, and Americas by 2023.

Eight countries account for two-thirds of the global TB burden:

1. India (20%)
2. Indonesia
3. China
4. Philippines
5. Pakistan
6. Nigeria
7. Bangladesh
8. Democratic Republic of the Congo

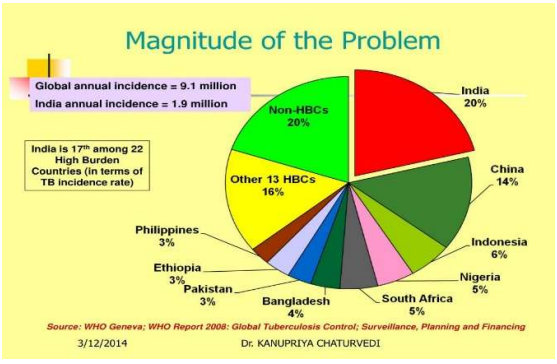


Fig 3: Magnitude of problem

Pathophysiology

After *Mycobacterium tuberculosis* (M. tb) enters the host, it reaches the lungs and is engulfed by macrophages. This triggers an immune response, attracting more immune cells to surround infected macrophages, forming a granuloma a hallmark of TB. In healthy individuals, granulomas keep the infection dormant, though reactivation is possible. M. tb survives by blocking phagolysosome fusion and modulating immune responses, allowing it to persist in a non- or slow-replicating state during latent TB.

Within granulomas, macrophages can transform into lipid-laden foamy macrophages. Their breakdown releases lipids, causing necrosis in the granuloma's center, forming caseum a cheese-like, soft material. This results partly from M. tb–induced disruption of lipid metabolism and the role of mycolic acids in foam cell formation [3]. Caseous granulomas serve as protective niches for dormant bacilli. Over time, the caseous core may soften and form cavities, enabling bacterial reactivation and active TB.

Reactivation risk increases with immunosuppression from HIV, malnutrition, certain medications, chemotherapy, uncontrolled diabetes, sepsis, substance abuse, chronic kidney failure, smoking, or cancer. When immunity wanes, dormant bacilli multiply, granulomas collapse, and cavities form, releasing infectious bacteria. The caseum also nourishes bacilli, promoting high bacterial loads and severe lung damage. Bacteria may spread via airways, bloodstream, or to other organs, making the disease contagious and symptomatic [4].

Granulomas in TB exist along a continuum:

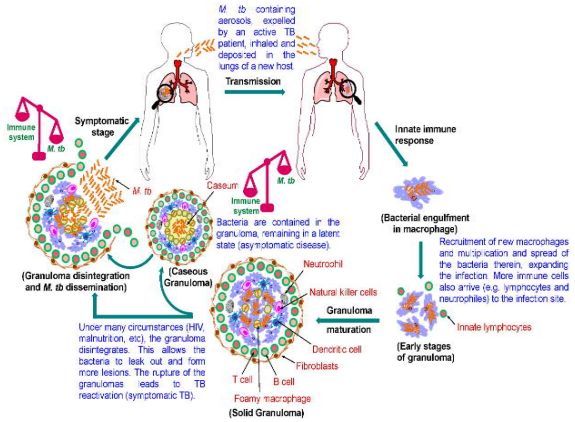


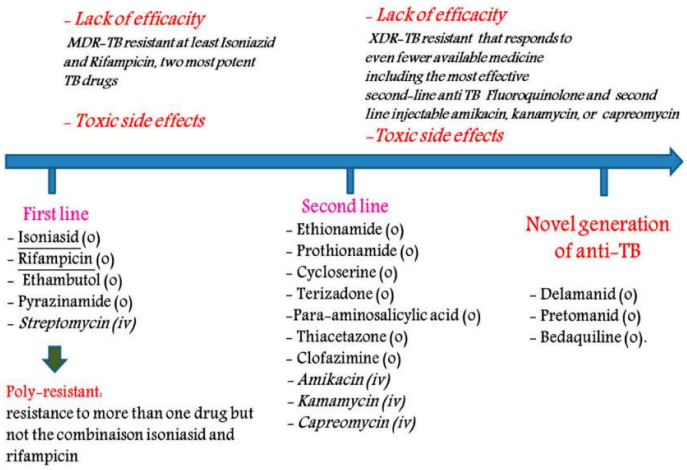
Fig 4: TB pathophysiology

Solid granulomas (early stage) lack necrosis, have a fibrotic wall, contain many immune cells (especially T lymphocytes), and harbour few bacilli typical of latent TB.

Necrotic granulomas show central cell death.

Caseous granulomas have necrotic, cheese-like cores with high bacterial loads, often linked to reactivation.

Classification of tuberculosis



Drug profile

Brand Names: Deltyba
Generic Name: Delamanid
Weight Average: 534.492
Chemical Formula:C25H25F3N4O6

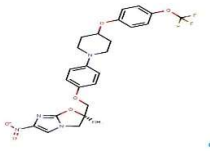


Fig 5: Str of delamanid

Background

Delamanid, a drug that inhibits the bacterial cell wall's synthesis of nitro-dihydro-imidazole, is an anti-tuberculosis agent. Treatment for multi-drug-resistant and extensively drug-reactive TB is achieved through a combination approach [(5)]. Patients suffering from tuberculosis with multidrug-resistant and extensively drug–reactive patients face clinical difficulties, including higher mortality rates and inadequate therapeutic response to standardized antitubercular therapy such as Isoniazid and Rifampin. A patient with tuberculosis that is resistant to multiple drugs may need more than 2 years of chemotherapy and second-line therapies with a narrow therapeutic index 4. Patients with pulmonary multidrug-resistant tuberculosis or extensively drug-resisted tubercula OS were treated with delamanid in a clinical study using WHO-endorsed drugs. Better treatment outcomes and a lower mortality rate were associated with an improved background treatment regimen 1.Treatment resulted in spontaneous resistance to delamanid, as a mutation in one of the 5 tested was observed. Bioactivation of delamanid is aided by the presence of F420 coenzymes [(6)]. Delamanid, an FDA-approved oral drug, is sold under the brand name Deltyba. It is distributed by Tokyo, Japan's Otsuka Pharmaceutical Co., Ltd.

Pharmacodynamics

In isolates of Mycobacterium tuberculosis, the minimum inhibitory concentration (MIC) of delamanid falls between 0.006 to 0.024 g/ml. Delamanid has the ability to kill M. kansasi and M.00 bovis, which are non-tuberculous mycobacteria that can be killed in vitro [(7)]. Delamanid lacks the capacity to fight off other antimicrobial drugs and shows no anti-tuberculosis efficacy in vitro against either Gram-positive or Gram-negative bacterial species. The reduction of Delamanid-measured tuberculosis colony numbers in chronic tubers were shown to be dose-dependent in murine models. The cardiac potassium channel (hERG channel) can be inhibited by repeated delamanid doses, leading QTc-prolongation, which is mostly brought on by delamanid's main metabolite, DM-6705.The results of animal experiments suggest that delamanid may reduce vitamin K-dependent blood clotting, enhance prothrombin time (PT), and activate partial lymphoma time (APTT) [(8)].

Mechanism of action

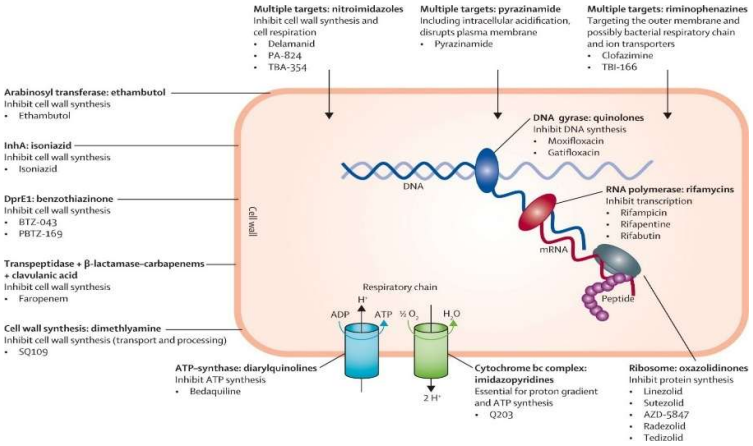


Fig 6: Mechanism of action

Delamanid is a pro-drug used to treat multi-drug-resistant tuberculosis (MDR-TB). It is activated by the *Mycobacterium tuberculosis* F420 coenzyme system, including Rv3547, a deazaflavin-dependent nitro reductase (Ddn). Genes like fgd and Rv3547 are linked to resistance. Upon activation, Delamanid is reduced to a desnitro-imidazole derivative, generating radical intermediates and reactive nitrogen species (RNS) such as nitric oxide. Its main action is inhibiting methoxy-mycolic and keto-mycolic acid synthesis, essential for cell wall integrity, leading to bacterial death. Unlike isoniazid, it does not target α-mycolic acids [(9)]. Radical intermediates also cause oxidative and nitrosative damage. Delamanid is given with other anti-TB drugs to enhance efficacy and prevent further resistance. Its unique, cell-wall–focused mechanism makes it a critical weapon against MDR-TB, effectively killing bacteria resistant to first-line agents like isoniazid and rifampicin while minimizing new resistance development.

CONCLUSION

Delamanid represents a significant advancement in the management of multidrug-resistant and extensively drug-resistant tuberculosis, conditions that continue to challenge global health systems. By uniquely targeting the synthesis of methoxy- and keto-mycolic acids in the bacterial cell wall, delamanid provides an effective mechanism to combat strains resistant to conventional first-line therapies. Clinical evidence highlights its ability to improve treatment outcomes, reduce mortality, and enhance the efficacy of WHO-recommended background regimens. However, risks such as spontaneous resistance due to genetic mutations and potential cardiac side effects, including QTc prolongation, underscore the need for careful patient monitoring and judicious use. Despite these limitations, delamanid stands as a valuable addition to the anti-tuberculosis armamentarium, offering hope in reducing disease transmission and advancing global TB control initiatives. Its integration into standard treatment strategies, alongside continued surveillance and research, will be essential to maximize its long-term clinical impact.

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