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Recent Innovations in the Inhalational Treatment of MDR TB: A Review

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A B S T R A C T

The lack of viable curative medicines for multidrug-resistant tuberculosis (MDR-TB) has an impact on both short-term and long-term worldwide efforts to eradicate MDR-TB. The purpose of this review is to discuss the advancement of inhalation medicines as a new approach to MDR-TB diagnosis and treatment, hence providing new options for patient care. Inhalation therapy is the most effective and localized form of medication treatment for the lungs, with the fewest systemic effects. The study gives an overview of a variety of inhalation devices, including nebulizers, dry powder inhalers (DPI), and metered dosage inhalers (MDI), and their use in the treatment of MDR-TB. Nanotechnology plays an important role in improving therapeutic efficacy and targeting. The review also highlights the progress made with new inhalation medications and therapeutic combinations, as well as the promising future of inhaled biologics and immunotherapy. Clinical studies have shown promise, but more study is needed to enhance drug composition, drug delivery methods, and treatment tactics in order to improve treatment and provide a better response to this health condition.

Keyword s : Tuberculosis, Multi drug resistant TB, Drug resistance.

Introduction:

Tuberculosis (TB) is one of the most common infectious diseases in the world, and it continues to pose a significant danger to healthcare systems, particularly in low- and middle-income nations. According to WHO, tuberculosis is a major public health concern, with an expected 10 million new cases in 2019 and 1.4 million deaths, making it one of the world's biggest infectious disease killers.[1,2] The impact of tuberculosis on healthcare systems is not one-sided. In resource-starved areas with inadequate health-care facilities, economically balanced population growth fights for tuberculosis treatment[1,3] Many nations with high tuberculosis prevalence, such as India, South Africa, and Indonesia, struggle to control the negative impact of TB cases on healthcare systems. [4,5] The fact that tuberculosis usually coexists with other diseases, such as HIV/AIDS, aggravates the situation by complicating care and increasing mortality rates.[6]

Furthermore, treating tuberculosis requires six months of at least one or more drugs. This necessitates a succession of health-care visits, which can strain already-strained health-care systems.[7] The demand for ongoing monitoring and follow-up may result in a shift of resources from other areas of the health system, having a broader impact on public health.[8]

WHO estimates that there would be 9.9 million newly diagnosed tuberculosis cases in 2023. Furthermore, the number of multidrug-resistant tuberculosis patients has increased, making treatment more difficult and expensive. Other articles have noted that this influence resulted in about 1.5 million TB-related fatalities in 2020, with HIV patients accounting for 214,000 of these deaths.[9]. The map depicts the uneven distribution of

tuberculosis incidence, highlighting the dominance of particular regions. According to the WHO, eight countries—India, Indonesia, China, the Philippines, Pakistan, Nigeria, Bangladesh, and the Democratic Republic of the Congo—account for two-thirds of the illness burden.[10]

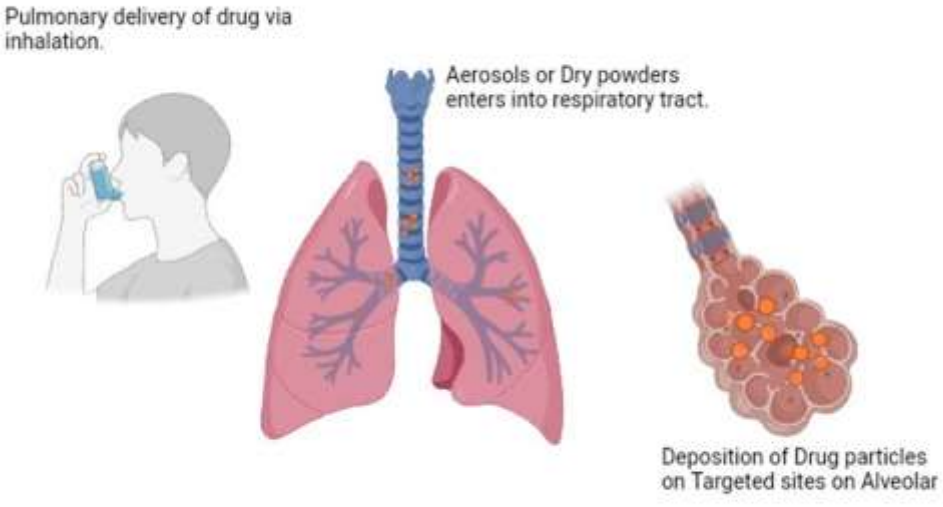

Figure 1 : Schematic representation of drug delivery via Inhalational route of administration Using Inhalational device .The drug particles are directly deposited on Alveoli of lungs.

In South Africa, the incidence is deemed worrying. According to estimates, the country's public health system faces significant challenges as a result of about 98-144 new tuberculosis infections per 100,000 people each year.[11] Mycobacterium tuberculosis causes multidrug-resistant tuberculosis. The most well-known and widely used first-line anti-TB medications are rifampicin and isoniazid.[12] There are several methods for mutation, and the rpoB niche contains rifampicin resistance mutations. The rpoB gene is situated in the RNA polymerases beta subunit locus, and its absence prevents the enzyme from binding to rifampicin, interrupting RNA synthesis.[13] The rpoB gene contains several frequent variants that confer rifampicin resistance in codons 516, 526, and 531. Numerous studies have identified these regions as containing such mutations, indicating a universal resistance level.[14]

Some people are resistant to isoniazid due to increased mutations in the katG gene. This gene encodes the enzyme catalase-peroxidase, which allows isoniazid to operate. We discovered multiple mutations in katG, particularly mutation 315, which resulted in a decrease of enzyme activity and subsequent drug activation. Furthermore, some modifications in the inhA promoter region result in resistance by altering the drug's target site. This increases the activity of the target rate-limiting enzyme, reducing the drug's effectiveness.[15,16]

These medications are key components of first-line TB therapy, and resistance complicates the disease's treatment. The rise of MDR-TB poses a hazard to public health since it leads to longer treatment duration, higher treatment costs, and greater morbidity and mortality.[17] Biofilm production is critical to the establishment and maintenance of a chronic TB infection. Biofilms, multicellular bacterial aggregates wrapped in a self-synthesized extracellular matrix, can form in Mycobacterium TB. This matrix provides a mechanism of protection that increases the bacteria's chances of survival against both the host's immune response and antibiotic therapy.[18]

Biofilms can lead bacteria to enter a latent phase, in which they are not actively proliferating and hence more resistant to treatments that target actively dividing cells. Dormancy of bacterial cells presents a significant difficulty in tuberculosis (TB) therapy since these cells might evade antibiotic treatments and then revive, resulting in treatment failure and disease recurrence.[19]The prevalence of MDR-TB is rising worldwide. According to World Health Organization (WHO) statistics, around 558,000 new MDR-TB cases were reported worldwide in 2017, with the majority occurring in areas with high TB burdens. MDR-TB is becoming more prevalent due to poor treatment methods, limited drug compliance, and the emergence of resistant strains [20, 21]. Treating MDR-TB presents challenges, including complex regimens. Patients with MDR-TB receive unjustifiably lengthy and/or intensive therapy. If resistant germs survive in the body uncontrolled, treatment failure can occur, prolonging the process. Experts recommend treating tuberculosis in six months, while MDR-TB can take 18-24 months—three to four times longer. Patients that are subjected to excessive complexity frequently have a high pain threshold, which is not necessarily appropriate. This can lead to noncompliance, poor management, and possibly move to uncontrolled treatment options.[22,23]

High costs: The expense of treating someone with MDR-TB is substantial. Drug-resistant tuberculosis strains must be treated with second-line anti-TB treatments, which are usually more expensive than first-line drugs. This can result in a large economic burden, particularly in developing countries where tuberculosis is endemic. Even in an ideal economy, TB medicine prices are very low; nevertheless, an MDR-TB case can result in treatment costs that are up to 100 times higher than those of a regular tuberculosis case. This economization also undermines WHO's attempts to eradicate the disease, as it can result in significant losses and inefficient resource allocation.Side effects: [24, 25]. Patients reported several side effects, including anemia, sadness, tinnitus, and introverted inclinations. The extensive unfavorable effects not only lengthen the duration of treatment, but also cause people to drop out of treatment programs, demonstrating that today's enforced adherence models simply exacerbate illness management. Some of these bad effects include nausea and vomiting, kidney impairment, and hearing loss, all of which can lead to noncompliance and complicate disease management.[26]

Although the oral route is a popular drug delivery method, it has certain drawbacks, especially when treating lung infections. Drug absorption is delayed because drugs taken orally must transit through the gut before entering the bloodstream. This extended method frequently delays the start of the effects. In cases of lung infections, where time is of the essence, this delay might greatly impede disease management.[27,28] Suboptimal Drug Concentrations at Infection Sites: When medications are administered orally, they enter the systemic circulation and may not reach the lungs at their peak concentration. The medicine circulates throughout the body, but its concentration in lung tissue may be quite low. This is especially concerning in cases of severe infections like multidrug-resistant tuberculosis (MDR-TB), because an effective treatment requires the medicine to be delivered at high local concentrations throughout the course of therapy.29,30

Unwanted Side Effects: Because oral drug absorption has a broad influence in the human body, administration via this manner can result in unintended side effects because the drug activity can affect other organs. A medicine that can effectively cure a lung infection may induce major side effects in other places of the body, calling into doubt the treatment's efficacy.[31,32]

Inhalational pathway is a solution.

The inhalational route provides an appealing alternative to oral treatment, especially for respiratory illnesses.

Enhanced local drug concentrations: As a method of drug administration, inhalation offers a unique opportunity to optimize local drug concentrations in the lungs. This method offers the advantage of reducing the drug's systemic exposure while assuring maximum effectiveness in the area that needs it the most. [33,34]

Rapid Treatment Action: Inhalers bypass the mouth and throat, allowing medication to reach the lungs and quickly diffuse and absorb through the alveolar membranes. Inhaled drugs have a fast onset of action, which is especially useful in acute conditions where a therapeutic effect is critical, such as in patients with severe respiratory problems.[35,36] Minimized Systemic Side Effects: Inhalational delivery focuses on focused drug delivery to the lungs and is associated with a lower risk of systemic adverse effects. The dosing of the chemical also reduces exposure to other organs, which improves the treatment's safety profile. According to research, inhaled medications enter the lungs quickly, resulting in low drug deposition in extrathoracic locations, which benefits pediatric patients.[37]

The lung architecture has a crucial role in medication distribution by inhalation. [38] The bronchial tree and alveoli provide a large area for effective drug absorption. Drug inhalation can settle particles in the lower lung, allowing the vascular system to absorb them.[39] Another important consideration is the size of the inhaled particles; bigger particles can clog the upper airways and limit lung absorption, whereas smaller particles can scatter during exhalation. Particulate matter having a diameter of 1-5 microns is ideal for deep lung penetration, allowing systemic absorption of the medicine once it reaches the alveoli. Early qualitative studies indicate that patients and healthcare providers may prefer breathed therapy over injectables. In a study of healthcare providers, a substantial proportion said that patients are likely to be eager to use inhalers, and many thought the devices were easy to use. [40]

There are various kinds of nebulizers:

Jet Nebulizers: These use a compressed air system to aerosolize liquid medications. These are often used in clinics to nebulize numerous types of medication, with the exception of oil-based formulations.[41] Ultrasonic nebulizers use high-frequency sound waves to administer medication as an aerosol. They are quieter and more portable than jet nebulizers, but they may be useless for treating some drugs.[42] Vibrating Mesh Nebulizers employ a thin mesh screen with small holes to create an aerosol mist of liquid solution.[43] They are effective and less wasteful, and they are often more portable than other types of nebulizers, making them appropriate for home use.[44] Dry Powder Inhalers (DPIs) use solid powder with medication particles instead of nebulized mist. They are portable and user-friendly, making them appealing to patients. Powder is then stored in an aerosolizer, which converts it into more dense particles that are deep-lunged for greater results.[45] One of the primary advantages of DPIs is that they function without propellants, making their design simple and their environmental impact small. Furthermore, DPI enables patients to achieve consistent dose without the need to coordinate actuation and inhalation, which can be challenging for patients using conventional inhalation devices.[46]

Metered dose inhalers (MDIs)

Metered dose inhalers, often known as compact pressured canisters holding the required pharmacological therapeutic layers in aerosol form, have just entered the market. Each actuation of an MDI strives to deliver a consistent quantity, making it extremely advantageous to the patient.[47] MDIs frequently use a propellant to aerosolize the medicine, allowing for more effective administration to the lungs. For chronic respiratory disorders, the issue of maintaining the correct dosage each time a medicine is given is more pressing and urgent.[48]

Recent advances in inhalational treatments for MDR-TB.

Many patients with drug-resistant tuberculosis (MDR-TB) can now get more consistent inhalation therapy. This is due to recent advancements in drug formulation processes, particularly those involving nanotechnology. Using metal ions, solid lipid nanoparticles (SLNs), polymeric nanoparticles, and other similar materials, researchers investigated a variety of methods for controlling how medications dissolve, remain stable, and are released. For example, SLNs can include hydrophobic medicines into their structures, enhancing bioavailability and using sustained release strategies to keep the medication at therapeutic levels for longer periods of time.[49,50]

Better nanocarrier deposition in the lungs: These nanocarrier systems can also alter crucial physical features that affect the effectiveness of aerosols and their ability to penetrate deep into the lungs and deposit medicines. By enhancing the therapeutic window of medications, such technologies can allow for a reduction in dose frequency, improving patient compliance with treatment regimens.[37]

Aerosolized anti-TB medications are available for inhalation. They include rifampicin, isoniazid, and bedaquiline, among others. This directtechnique allows for drug delivery at the site of infection, boosting therapeutic effectiveness while decreasing the detrimental impact on other body systems. The use of inhaled formulations can result in increased local medication concentrations, which can be beneficial in the treatment of MDR-TB.[51,52]

Another potential strategy for combating drug-resistant bacteria is to create inhalation combination treatments. These medications function by concurrently targeting numerous bacterial pathways, increasing therapeutic efficacy and lowering the risk of bacterial resistance. For example, utilizing bedaquiline in conjunction with its replacements, such as linezolid, produces a combination effect that improves treatment reliability.[53]They developed an inhalation treatment that delivers LNZ gradually, can pass through mucus, and is generally safe at therapeutic levels. This shows that it could be an effective treatment for pulmonary tuberculosis, but further research is needed on particle size, zeta potential, and drug release qualities before it can be utilized in humans. LNZ-NLCs are a medication delivery technology that outperforms many existing approaches.[54-56]

Conclusion:

Inhalation treatments show great promise for transforming MDR-TB treatment. Their capacity to deliver medications directly to the lungs, reduce systemic side effects, and increase patient adherence makes them a more compassionate and effective alternative to existing oral regimens. Despite substantial advances, further research is needed to improve drug compositions, delivery methods, and treatment tactics. A truly patient-centered strategy necessitates not only scientific innovation but also a thorough awareness of patient requirements, ensuring that these breakthroughs result in improved health outcomes and a higher quality of life for patients living with MDR-TB.

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