

# Time to Reconsider the Inhaled Drugs for Tuberculosis

Sir,

Tuberculosis (TB) is a potentially severe infection. It is a major public health issue in developing countries. The alarming rise of multidrug-resistant (MDR) and extended drug-resistant (XDR) TB creates a need to resurface the idea of exploring alternate modalities of anti-TB drugs. The incidence of TB is reducing worldwide but not at the pace to attain the milestone of a 20% decrease between 2015 and 2020.<sup>1</sup> The real threat to this achievement is drug-resistant TB. According to World Health Organisation (WHO) Global Tuberculosis report 2020, MDR-TB patients have a success rate of 54% and XDR-TB of only 30%.<sup>1</sup> MDR and XDR-TB are spreading at an unstoppable speed, and developing countries are their main target. The upward surge in MDR and XDR-TB incidence and scarcity of non-tuberculosis mycobacterium (NTM) specific treatment have renewed interest in inhaled mycobacterial therapies for lung disease. Inhaled medicines can boost the therapeutic concentration of drugs in the lungs, limiting overall systemic exposure and reducing off-target side effects of the treatment.<sup>2</sup> Aerosol streptomycin used in the treatment of 12 TB children showed no symptoms of toxicity. Of these, nine children revealed "healing," characterized by a decrease in size or complete removal of granulomas from the lung tissue.<sup>3</sup> In refractory TB patients, Sacks *et al.* studied the inclusion of inhaled kanamycin and gentamicin in guidelines-based therapy (GBT). They found out that 68% of patients got their sputum converted within 33 days (mean time-to-conversion).<sup>4</sup>

A recent study of aerosol capreomycin in guinea pigs revealed tissue levels in lungs substantially more than the minimum inhibitory concentration (MIC) and enhanced drug collection in multiple-dose trials.<sup>5</sup> This approach significantly decreases the bacterial load proving greater efficacy compared to traditional parenteral methods. It has been found effective in conventional drugs like isoniazid, rifampin, and rifabutin as well since drug particles are absorbed by alveolar macrophages, and the concentration of drug inside macrophages brings the effect. Aerosol trials of these dry-powder formulations revealed that all preparations exhibited a tiny fraction of particles and aerosol properties compatible with inhaled administration.<sup>6</sup> Moreover, the nebulised formulation drugs generate aerosol particles within a respirable range and optimise medication delivery to the lungs. The benefits of the intrapulmonary administration modality on local and systemic pharmacokinetics illustrate how inhaled treatment can reach high levels in the lungs while keeping low systemic levels, leading to reduced toxic effects. Different experiments performed on traditional drugs and other drugs like azithromycin, colistin, and clofazimine have shown promising results.<sup>6,7</sup>

The course of anti-TB therapy is already very long. MDR and XDR-TB increase the risk of non-compliance, adding to the patient's misery and dulling the quality of life (QOL). However, directly observed therapy, short course (DOTS) is the standard strategy for TB treatment, but its outcomes are equivocal. In addition, due to the inconvenience of laborious and time-consuming DOTS, the discovery of new inhaled drugs becomes the need of the hour. Inhaled therapy opens the door to an alternate form of primary as well as adjuvant treatment for TB. We should investigate options that will extend the life expectancy of TB patients and improve their QOL. Inhaled treatments for TB are potentially beneficial techniques that need further testing in clinical trials. These could offer comparable efficacy with reduced side effects. Why put it off any longer? Inhaled drugs should be taken forward right away based on the above in-vivo animal and human investigations.

## COMPETING INTEREST:

The authors declared no competing interest.

## AUTHORS' CONTRIBUTION:

UK: Idea and writing. AG: writing. FA: Reviewing and proof-reading. All authors approved the final version of the manuscript to be published.

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