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The World must Seriously Consider with Urgency the Use of Thioridazine in Combination with Conventional Antibiotics for Therapy of Extensively Drug Resistant Pulmonary Tuberculosis: Therapy Proven Effective in Argentina

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Summary

During the 1950's, the consensus among infection disease practitioners was that pulmonary tuberculosis, as a consequence of the effectiveness of the two main anti-tuberculosis drugs, isoniazid (INH) and rifampicin (RIF), would soon be globally eradicated. However, as a consequence of civil unrest, wars, poverty and famine primarily in third world countries, the incidence of tuberculosis infections increased dramatically in these countries and what was once a curable infection, became frequently resistant to INH and RIF termed multi-drug resistance tuberculosis (MDR-TB) as a consequence of poor delivery of therapy, ineffective therapy and patient non-compliance. By the late 1980's, the emergence of HIV/AIDS contributed further to the escalation of TB especially in Western countries and coupled to large numbers of migrants infected with Mycobacterium tuberculosis, the causative pathogen of pulmonary tuberculosis, that settled in the major cities of Western countries and later presented with active tuberculosis, the incidence of pulmonary TB reached critical levels, especially in New York City where the incidence quadrupled and more than half of the isolates of the infecting bacterium exhibited an MDR phenotype. It soon became clear MDR-TB was a dire threat to global health and because MDR-TB produces a high percentage of mortality, the need for effective drugs was urgent. However, for a variety of reasons, the pharmaceutical industry did not respond, and the only anti-TB drugs that were available termed second-line of defence drugs, produced high incidence of morbidity, and for the most part, where support for therapy of TB is poor or non-existent, their effective use was limited due to costs and MDR-TB patients were treated poorly and multi-drug resistance evolved to higher levels of resistance such as extensively drug resistant TB (XDR-TB), and in the last two years, especially in India, resistance progressed to the level where the infective organism was resistant to all known and available anti-TB drugs (TDR-TB). At the time of this writing, with the exception of one agent in combination with anti-TB drugs to which the infective bacterium was initially resistant, there are in effect no drugs that can effectively treat XDR-TB and certainly TDR-TB. It is the purpose of this Editorial to present the proven potential of the old phenothiazine neuroleptic Thioridazine (TZ) in combination with commonly available anti-TB drugs for the therapy of XDR and most likely TDR-TB.

TZ has in vitro activity against all encountered Mtb regardless of its antibiotic resistance status [1-3]. However, the activity takes place at concentrations of TZ that well exceed its toxic level in the human. Nevertheless, TZ induces the killing of phagocytosed MDR-Mtb and XDR-Mtb by non-killing macrophages at concentrations which are well within the limits of its toxic range in humans [4-6]. These latter studies were followed by a number of independent studies that demonstrated that TZ can cure the mouse of a pulmonary TB infection either by itself as monotherapy or in combination with antibiotics [7-9]. Finally, TZ when used in combination with antibiotics to which the initial infective XDR-Mtb strain was resistant, 17 XDR-TB patients were cured [10,11]. TZ has also been used as a salvage drug for XDR-TB patients, i.e. it improved the quality of life of XDR-TB patients (restored appetite and patients gained weight, obviated night time sweats, and reduced stress associated with a terminal condition) and as has been the case with its use for combinational therapy of XDR-TB, it does not produce any cardiopathology when the patient is properly monitored [12]. These successes demonstrate that TZ has the potential to cure XDR-TB, it is safe to use, it is cheap and must be seriously considered by countries such as India that have a huge XDR-TB load and now present with increasing numbers of TDR-TB cases [13]. The global health community must heed its use for therapy of pulmonary TB infections that are beyond current therapeutic effectiveness.

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