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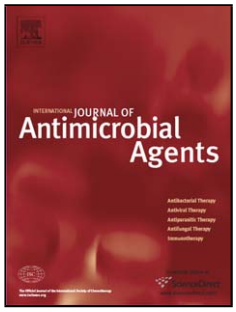

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Thioridazine cures extensively drug-resistant (XDR-TB) and the need for global trials is now!

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ABSTRACT

Thioridazine (TDZ) has been shown to have in vitro activity against multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains of *Mycobacterium tuberculosis*, to promote the killing of intracellular MDR and XDR strains and to cure the mouse of antibiotic-susceptible and -resistant pulmonary tuberculosis (TB) infections. Recently, TDZ was used to cure 10 of 12 XDR-TB patients in Buenos Aires, Argentina. At the time of writing, it is being used for the therapy of non-antibiotic-responsive terminal XDR-TB patients in Mumbai, India, on the basis of compassionate therapy and although it is too early to determine a cure, the patients have improved appetite, weight gain, are afebrile and free of night sweats, and their radiological picture shows great improvement. Because XDR-TB is essentially a terminal disease in many areas of the world and no new effective agents have yet to yield successful clinical trials, global clinical trials for the therapy of XDR-TB are urgently required.

1. Introduction

Pulmonary TB is an infectious disease caused by *Mycobacterium tuberculosis*, which by its co-evolution with man became a steadfast human pathogen when man converted from a hunting-gathering animal to a land-dependent primate. The prevalence and impact of TB is exacerbated by poverty, overcrowding, famine, war and disease. More recently, diseases that reduce the effectiveness of the immune system, such as human immunodeficiency virus (HIV) infection, predispose the patient to progress from infection to active disease status. In the post-World War II years, especially in the late 1950s, progress in living conditions in the Western world and the introduction of antituberculous drugs fed the dream that TB could finally be eliminated. Progress was made and the number of new TB cases dwindled to a few per hundred thousand persons in most high income nations. In most low income settings, especially those blighted by war or famine, TB remained unchecked. Although the downward trend among the European- or US-born continued, TB among foreign-born individuals increased significantly during the 1970s, reaching still higher levels during the 1980s, 1990s and 2000s [1]. At first, although TB was found almost exclusively in the migrant population, it soon also increased among nationals, especially those who were co-infected with HIV and presented symptoms of acquired immune deficiency syndrome (AIDS). By 1992, the scale of new cases of TB infection noted for the city of New York had quadrupled, and of greater alarm was that more than one-half of these new cases of active TB were resistant to the two most effective drugs, isoniazid (INH) and rifampicin (RIF), defined as multidrug-resistant TB (MDR-TB) [2]. By the

middle of the 1990s, similar observations were made for each of the main urban centres of Europe [1], although the magnitude of the problem was far less than that experienced in New York City. With huge financial support, the TB control programmes developed in New York took care of the problem within 3 years and the incidence of new cases of active TB was reduced to a lower level than recorded in the 1950s [3]. In contrast, in other countries the rates of MDR-TB among new cases continued to increase and the spectrum of drugs to which the strains were resistant also increased [4]. In 2006, the term ‘extensively drug-resistant TB’ (XDR-TB) was introduced to define resistance to INH and RIF (i.e. MDR) and additionally to any fluoroquinolone and at least one of the three injectable antituberculous drugs amikacin, kanamycin and capreomycin [4]. Retrospective analysis of MDR strains from Portugal showed that >50% of all MDR strains are in fact XDR [5]. Data from India reveals that ca. 10% of MDR-TB strains are XDR. In Europe, ca. 10% of the 2500 MDR-TB cases occurring in the period 2003–2006 in fact represented XDR-TB [4], but this was strongly associated with former Soviet Union States. These data suggest that the problem of XDR-TB is long-standing but has been unrecognised until the publicity associated with an outbreak of XDR-TB in South Africa, mainly among HIV-positive individuals. Although the extent of the XDR-TB problem is unknown, anecdotal evidence suggests that significant problems exist in all urban centres of Europe, most acutely in some Eastern European countries and in India [4]. Recently, Velayati et al. [6] reported from Iran new forms of totally drug-resistant TB and coined the phrase ‘super extensively drug-resistant tuberculosis’.

If the healthcare community is to be successful in controlling this threat, we urgently need better tools for diagnosis and treatment as an effective vaccine is still far in the future. To support the efforts of TB control programmes we must shorten the duration of treatment. Shorter regimens may improve adherence and completion rates, reducing the opportunity for acquisition of new resistance. However, therapy of the MDR-TB patient is problematic and even with the best possible support [laboratory, directly observed treatment, short-course (DOTS), etc.] and regardless of aggressive therapy involving at least seven or eight drugs, mortality is significant (ca. 15–20%). This is considerably higher if the MDR-TB patient is co-infected with HIV and presents with AIDS. Therapy of the XDR-TB patient is even more difficult. There remains an urgent unmet need for new drugs to manage existing patients with MDR- and XDR-TB. The progress that has been made since the Cape Town Declaration is promising and a TB drug pipeline exists, but the rate at which new molecules will trickle down means that progress will come too late for the hundreds of thousands of current patients struggling to survive their XDR-TB. Moreover, at the time of writing, no clinical trials for therapy of XDR-TB with new agents are taking place (http://clinicaltrials.gov/ct2/results?term=XDR+Tuberculosis). Consequently, there is no completely effective therapy available, apart from the one that we will describe in this article.

2. Thioridazine (TDZ): a promising development

TDZ, a neuroleptic used for the therapy of psychosis, has been safely in use for over four decades. TDZ is an example of a drug that has passed beyond patent protection and is of little interest to the pharmaceutical industry for future development since it offers no promise of financial reward. TDZ has been shown to inhibit in vitro growth of all *M. tuberculosis* strains studied to date regardless of their antibiotic susceptibility profile [7]. TDZ enhances the killing of intracellular *M. tuberculosis* by non-killing human macrophages including susceptible, MDR and XDR strains [8,9]. TDZ cures the mouse of infections with antibiotic-susceptible [10] and MDR (unpublished data) strains.

TDZ was used for the therapy of XDR-TB patients who did not respond to any antibiotic therapy and whose prognosis was poor and hence were selected for TDZ therapy on the basis of compassionate reasons [11]. As predicted, TDZ cured 10 of 12 XDR-TB patients and the remaining 2 patients responded favourably but dropped out of the programme [11]. However, as is the case for any neuroleptic [12], there are patients whose QTc interval is significantly increased thereby placing the patient at risk for sudden death [12]. Because patients can be screened with cardiac monitoring prior to and during initial therapy with TDZ, the problem can be minimised and even avoided.

TDZ is ready for global clinical evaluation. It is the only effective drug that has been studied for its antituberculous properties in a systematic fashion—from its

activity within a test tube culture to its activity at the site where *M. tuberculosis* resides, namely the macrophage and its curative activity against antibiotic-resistant pulmonary TB infections of the mouse and human. TDZ is ready for global clinical trials if only because it is ready for deployment now and may prolong the life of or cure tens of thousands who are infected with a terminal XDR-TB infection.

3. Compassionate therapy of extensively drug-resistant tuberculosis in India with thioridazine

India bears the burden of most of the worlds MDR-TB. In the latest global drug resistance report [3], India accounted for one-third of the world's MDR-TB cases. There is no public provision for treating these patients who visit multiple public and private medical practitioners in a desperate attempt to treat their drug-resistant TB, most serving merely to amplify their resistance further. A huge pool of chronic drug-resistant patients is created and it is not uncommon to see patients who are resistant to all known antituberculous agents [13]. At Hinduja Hospital (Mumbai, India), we received ethics committee approval to proceed with a trial involving addition of TDZ on a 'compassionate use basis'. Eight patients with XDR-TB who remained persistently sputum smear- and culture-positive despite 1 year of second-line drugs have been enrolled to receive TDZ in escalating doses. Baseline cardiac status and regular monitoring for QTc prolongation were and will be performed throughout the duration of the study. It is hoped that this study will pave the way for larger collaborative studies with TDZ in

patients with XDR-TB who have exhausted all available drug options. At the time of writing, all the patients have tolerated daily doses of 75 mg TDZ during the first 6 weeks of therapy with encouraging results in terms of clinical well-being (cessation of coughing, afebrile, regaining loss weight, etc.). Sputum culture reports are awaited.

In this era of MDR- and XDR-TB, we need a smart drug development programme for clinical evaluation of potential antituberculous drugs in parallel [14]. In the specific case of TDZ, the approach can be tailor-made: since there is such a long clinical experience with this drug, a combined phase I and II study in normal sensitive TB patients with assessment of early bactericidal activity at increasing dosages can be designed. A small phase II study looking at safety and tolerability as well as evaluation of serial sputum colony counts [15] for TDZ in combination with a standard regimen in normal sensitive TB can follow. Consecutively, there should be a ‘smart’ trial design in MDR- or XDR-TB patients in two groups: a control group receiving best care and a trial group receiving best care plus TDZ (Tibotec model presented at the 46th Interscience Conference on Antimicrobial Agents and Chemotherapy, 2008). There are several sites in Africa and Asia that have developed or are in the process of developing clinical research capacity to make these kinds of approaches feasible.

In conclusion, there is a pressing need to evaluate drugs such as TDZ in clinical trials for the therapy of XDR-TB as described above. To conduct these global

trials there is the need to create international laboratories to serve as centres for rapid identification of XDR-TB patients and that can accurately characterise the resistance spectrum. The situation is urgent; we must work fast and secure the support needed to perform international standard regulatory studies that will influence TB programmes. Thus, we must create the political will within each country, as support from the respective governments and their health agencies is vital for any success. It is the responsibility of the whole healthcare community to support endeavours to develop new treatments for XDR-TB urgently. Please join us and the supporters of global trials for therapy of XDR-TB identified in this article.

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None declared.

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