Bedaquiline: First FDA-approved tuberculosis drug in 40 years

The US Food and Drug Administration (FDA) on 28 December 2012 granted accelerated approval to Johnson and Johnson's drug bedaquiline to treat resistant tuberculosis (TB), more prevalent in India, China and Eastern Europe.[1] TB remains a global epidemic, with over 2 billion people harboring latent infection and more than 9 million new cases, of which 500,000 are multidrug-resistant (MDR), and nearly 2 million deaths are estimated to occur each year.[2] This mandates discovery of new drugs with novel mechanisms of action to not only shorten the duration of treatment of drug-sensitive TB, but also for treatment of MDR-TB.

TB is a highly infectious disease and is considered one of the world's most serious public health threats. A study in September 2012 published in The Lancet found that almost 44% of patients with TB in countries like Russia, Peru and Thailand showed resistance to at least one second-line drug, or that a medicine used after another drug had already failed. Treating drug-resistant TB can take years and can cost 200 times as much as treating the ordinary form of the disease. Bedaquiline approval was the first time in 40 years that the agency had approved a drug that attacked TB in a different way from the current treatments on the market. The drug, to be called Sirturo, was discovered by scientists at Janssen, the pharmaceuticals unit of Johnson and Johnson, and is the first in a new class of drugs that aims to treat the drug-resistant strain of the disease.[3]

Bedaquiline's unique and specific anti-mycobacterial activity derives from inhibition of the proton pump of mycobacterial ATP synthase. ATP synthase is a critical enzyme in the ATP synthesis of *M. tuberculosis*. Binding of bedaquiline to the oligomeric and proteolipic subunit-c of mycobacterial ATP synthase leads to inhibition of ATP synthesis, which subsequently results in bacterial death. The gene encoding the subunit-c of the ATP synthase is denoted as atpE and its amino-acid sequence is highly conserved in non-related *M. tuberculosis* isolates.[2]

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However, the drug's potential risks, including increased risk of death, have raised concerns among members of the FDA. About 11.4% of patients taking Sirturo died during clinical trials compared with 2.5% of those taking placebos. As the drug carries some significant risks, it is mandated to be used only in patients who do not have other treatment options.[1] Sirturo carries a so-called black box warning for patients and healthcare professionals that it can affect the heart's electrical activity causing prolongation of the QT interval, which could lead to an abnormal and potentially fatal heart rhythm. Accordingly, the FDA has approved bedaquiline as part of combination therapy to treat adults with MDR pulmonary TB when other alternatives are not available. The FDA also granted fast-track designation, priority review and orphan-product designation to bedaquiline.[4]

The safety and effectiveness of bedaquiline were established in 440 patients in two phase-2 clinical trials. Patients in the first trial were randomly assigned to be treated with bedaquiline plus other drugs used to treat TB, or a placebo plus other drugs used to treat TB. All patients in the second trial received bedaquiline plus other TB drugs. Both studies were designed to measure the time taken for a patient's sputum to be free of *M. tuberculosis*, known as sputum culture conversion. Results from the first trial showed that patients treated with bedaquiline combination therapy achieved sputum culture conversion in a median time of 83 days, compared with 125 days in patients treated with placebo combination therapy. Results from the second trial showed that the median time to sputum culture conversion was 57 days, supporting the efficacy findings of the first trial. Common side effects identified in the clinical trials included nausea, joint pain and headache.[4]

The company said that although commercial opportunity is very limited, it expects to begin selling bedaquiline in the second quarter of 2013, and will not announce its sales price until then.[1] So, let us keep our fingers crossed!!

Rajiv Mahajan

Department of Pharmacology,
Adesh Institute of Medical Sciences and Research,
Bathinda, Punjab, India

Address for correspondence: Dr. Rajiv Mahajan,
Department of Pharmacology,
Adesh Institute of Medical Sciences and Research,
Bathinda - 151 101, Punjab, India.
E-mail: drrajivmahajan01@yahoo.co.in

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