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Editorial

After 40 years, new medicine for combating TB

On December 31, 2012, the FDA approved the first new tuberculosis drug in four decades. SIRTURO™ (bedaquiline) was approved on the basis of phase two efficacy and safety data to treat multidrug-resistant tuberculosis (MDR-TB). Bedaquiline is manufactured by Johnson and Johnson and is the first medication exclusively manufactured for MDR-TB [1].

An estimated 630,000 cases of MDR-TB (range 460,000–790,000) were reported throughout the world in 2011. Of all tuberculosis cases, 3.7% of new cases and 20% of previously treated cases are estimated to be MDR-TB. A disproportionately high number of MDR-TB cases are in India, China, the Russian Federation and South Africa, accounting for 60% of the MDR-TB prevalence in the world. In 84 countries, there have been reports of a higher resistance category known as extensively drug-resistant TB, or XDR-TB, making up around 9.0% of the average proportion of MDR-TB cases [2].

Bedaquiline is a diarylquinoline component with a new mechanism of action against *Mycobacterium tuberculosis* (MTB) *which specifically inhibits mycobacterial adenosine triphosphate (ATP) synthase [3,4]. It is suggested that bedaquiline forms a wedge between the two rotating subunits of ATP synthase by interacting with the residues W15 and F50 of* ε and the c-ring, respectively [5].

Bedaquiline inhibits drug-sensitive and drug-resistant MTB. Also, treatment courses including bedaquiline are likely to shorten the duration of TB therapy [6]. Further, bedaquiline has different extracellular and intracellular effects which are believed to enhance its effectiveness. The bactericidal activities of bedaquiline in a liquid culture medium started with a bacteriostatic phase lasting about 7 days and then continued with a dose-related bactericidal phase. However, the intracellular activity of bedaquiline is clearly greater than its extracellular activity mainly because the preliminary static phase was shorter or absent [7].

Bedaquiline may also impact current treatment approaches for latent TB infection (LTBI). This is especially true for the LTBI treatment for close contacts of patients with drug resistant TB. There is a lack of a practical and standard approach to LTBI treatment among contacts of patients with MDR/XDR-TB (DR-LTBI). In a murine model, bedaquiline demonstrated bactericidal activity against dormant (non-replicating) tubercle bacilli with substantial sterilizing activity and may enable treatment of DR-LTBI in 3–4 months [8].

Preliminary data for bedaquiline is encouraging for clinicians who treat TB infections. Given the increasing common treatment challenges of evolving resistance patterns coupled with a lack of major developments in TB treatment regimens, the development of this new agent has left many optimistic. Future use of bedaquiline is believed to shorten treatment courses and improve cure rates of MDR-TB and perhaps XDR-TB. Currently, treatment of drug-resistant tuberculosis requires second-line anti-TB drugs that are less effective with high adverse reaction profiles, and treatment courses can exceed as long as 2 years. Therapy for MDR-TB represents a major driver of healthcare and public health resources in that treatment courses are long and costly, adverse events are common, and failure rates as well as relapses are common [9].

FDA approval of bedaquiline was based on extremely encouraging data reported from two phase II clinical trials. The first study was a multicenter, placebo-controlled study of 47 patients with a confirmed diagnosis of MDR-TB with an 8-week follow-up [10]. Of the 47 patients evaluated, 23 were randomly allocated to the case group with bedaquiline and 24 received a placebo. Patient medication adherence was at least 97% in both groups. Patients treated with bedaquiline outperformed in both clinical outcomes in non-clinical measures. For example, conversion from positive to negative sputum cultures occurred much more rapidly in the bedaquiline arm. The conversion rate to a negative culture was 48% and 9% in the case and placebo group, respectively. There were no premature discontinuations due to adverse events associated with treatment in both groups, and side-effect profiles were similar in the two treatment groups, including nausea, joint pain, and headache. This study also established diarylquinolines as a new drug class with safe and effective profiles in humans as well as animals. Recently, a 2-year follow-up of this study was published concluding that bedaquiline might improve multidrug-resistant tuberculosis treatment by more rapid conversion of positive sputum to negative and preventing acquired resistance to other administered anti-TB agents [11].

The second trial was presented at the 43rd Union World Conference on Lung Health in Kuala Lumpur 2012 [12]. A total of 161 patients were included in the study. The patients with newly confirmed MDR-TB were randomly divided into the bedaquiline group (79 subjects) and the placebo group (81 subjects). The bedaquiline group received bedaquiline 400 mg by mouth daily for 14 days and then 200 mg orally three times a week. Both groups received a preferred 5-drug background regimen consisting of: Ethionamide, Pyrazinamide, Ofloxacin,

Kanamycin and Terizidone/Cycloserine. The study analysis showed more QT prolongation in the bedaquiline group than placebo, with no reports of serious cardiac arrhythmias such as ventricular tachycardia or Torsade de pointes. The bedaquiline group had a faster culture conversion to negative within 24 weeks and a higher sputum conversion rate (79% vs. 58%) at the end of 24 weeks.

Despite these promising results, the overall benefit of bedaquiline remains unproven. First, bedaquiline metabolized by a Cytochrome P-450 system (CYP3A4) is strongly induced by Rifampin. Therefore, bedaquiline is not recommended to be co-administered with agents in the Rifamycin family, which remains a common agent for TB treatment. Also, the manufacturer advises that co-administration with strong systemic CYP3A4 inhibitors for more than 14 consecutive days should be avoided. More information is available at the Johnson and Johnson website [13]. Thus, it would not be suitable for drug-sensitive TB. Second, bedaquiline prolongs the QT interval in electrocardiogram (ECG) [14]. Consequently, co-administration of any drug that increases the QT interval should be avoided.

Third, the manufacturer reports an increased risk of death associated with the bedaquiline treatment group (11.4%) compared with the placebo treatment group (2.5%) in one placebo-controlled trial. Although the reason for increasing mortality in the bedaquiline group is unclear, it should be advised that bedaquiline use should be limited to those patients with whom an effective treatment regimen cannot otherwise be provided.

Clearly, further studies are required to determine the role of bedaquiline in TB management. As a condition of submission under accelerated FDA approval, Johnson and Johnson is obligated to conduct a confirmatory phase III study, which is planned to begin soon. In this phase III study, there is hope that some of the questions regarding both safety and efficacy will be answered. First and foremost, the potential risk of mortality needs to be well understood before bedaquiline can have any role in patient care. Also, research needs to establish a well-proven combination therapy regimen for the treatment of MDR-TB, and the activity of bedaquiline in XDR-TB also needs to be studied. Human studies are needed to show the role of bedaquiline in DR-LTBI. Finally, further analysis is needed to understand the implications of bedaquiline in MDR-TB and HIV co-infection.

Conflict of interest

None declared.

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