Bedaquiline: A stepping stone in Multidrug resistance of Tuberculosis Disease

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Received 14 December, accepted 18 January, published online 01 February, printed 16 February 2013

ABSTRACT

Bedaquiline has become the first drug to be approved in the US for the treatment of multi-drug resistant tuberculosis (TB).The condition arises when Mycobacterium tuberculosis, the bacteria that cause TB, develop resistance to isoniazid and rifampicin, two key drugs for TB treatment. Bedaquiline helps by inhibiting an enzyme the bacteria need to replicate and spread through the body. The drug has been approved through the ‘accelerated approval’ process, which puts drugs on the market earlier than would otherwise be possible while the companies continue to collect clinical trial data. It was developed by Janssen Therapeutics, a subsidiary of US healthcare giant Johnson & Johnson. The company says bedaquiline is the first TB drug with a new mechanism of action for 40 years.

1. INTRODUCTION

Bedaquiline (also known as Sirturo, TMC207 or R207910) is a diarylquinoline anti-tuberculosis drug, which was discovered by a team led by the Belgian Koen Andries at Janssen Pharmaceutica. It was described for the first time in 2004 at the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) meeting Late-Breaker Session, after the drug had been in development for over seven years, and a trial of 47 patients showed that it is effective in the treatment of M. tuberculosis. It is the first new medicine to fight the infection in more than forty years. Sirturo is the first medicine specifically designed for treating multi-drug-resistant tuberculosis — an increasingly common form of the disease that cannot be treated with at least two of the four primary antibiotics used to treat tuberculosis. The standard drugs used to fight the disease were developed in the 1950s and 1960s.

Roughly one-third of the world’s population is estimated to be infected with the bacteria causing tuberculosis. The western media flashed a news report early this month stating that the US FDA approved a new drug, bedaquiline, for the treatment of multidrug resistant tuberculosis giving hopes to millions of patients suffering from the disease around the world. The FDA approval for a new TB drug, actually a combination of a few drugs, came after more than 50 years. The drug was discovered by scientists at Janssen, the pharmaceuticals unit of Johnson & Johnson, and is claimed to be the first of a new class of drugs that aims to treat the drug-resistant strain of the disease. The FDA approved bedaquiline under an accelerated programme that allows the agency to conditionally approve drugs that are viewed as filling unmet medical needs with less than the usual evidence that they work. The drug’s approval was based on studies that showed it killed bacteria more quickly than a control group taking the standard regimen, but it did not measure whether in the end patients would actually benefit from bedaquiline. Johnson & Johnson is, therefore, expected to conduct larger clinical trials to investigate whether the drug performs as predicted.

2. ABOUT THE DRUG

2.1. Classification

- Antitubercular Agent
- Diarylquinoline antimycobacterial

2.2. Dosing

**Adult**

Weeks 1-2: 400 mg PO qDay for 2 weeks, then Weeks 3-24: 200 mg 3 times/week for 22 weeks

**Pediatric**

<18 years: Safety and efficacy not established

2.3. Mechanism of Action

- Inhibits mycobacterial adenosine 5′-triphosphate (ATP) synthase

2.4. Pharmacodynamics/Kinetics

- Half-life elimination: 5.5 months
- Renal clearance: <0.001%
- Excretion: Mainly in feces
- Peak Plasma Concentration: 5 hr
- Bioavailability: Increased 2-fold when taken with standard meal compared with fasted conditions

Balasubramanian et al., Bedaquiline: A stepping stone in Multidrug resistance of Tuberculosis Disease, Discovery Pharmacy, 2013, 3(8), 14-16, www.discovery.org.in/dp.htm
PHARMACY OF THE MONTH

- Metabolized primarily by CYP3A4

2.5. Indications
- Treatment of pulmonary multidrug-resistant tuberculosis in combination therapy when other alternatives are not available.
- Should not be used for latent, extrapulmonary or drug-sensitive tuberculosis.
- Take with a multidrug regimen consisting of at least 4 other drugs that the MDR-TB is likely susceptible for the entire 24 week duration
- Reserve for use when an effective treatment regimen cannot otherwise be provided.

2.6. Contraindications
- None

2.7. Adverse Effects
- Nausea (38%), Arthralgia (32.9%), Headache (27.8%), SGOT, SGPT increased (8.9%), Blood amylase increased (2.5%), QT prolongation
- Increased risk of death due to QT prolongation
- Hepatic-related adverse effects increased when bedaquiline added to multidrug regimen; avoid alcohol and other hepatotoxic drugs

2.8. Pregnancy
- Classified as Pregnancy category B

2.9. Lactation
- Not known if bedaquiline is excreted in breast milk

2.10. Drug Interactions
- Decreased Bedaquiline Levels : rifampin, rifapentine, rifabutin (strong CYP3A4 inducers)
- Increased Bedaquiline Levels : CYP3A4 inhibitors

Monitoring
- Monitor ALT, AST, Alkaline phosphatase, and bilirubin at baseline, and monthly while on treatment
- Prolongs QT interval; obtain ECG before initiating treatment and at least 2, 12, and 24 weeks after starting treatment
- Obtain baseline serum levels for potassium, calcium, and magnesium and correct if abnormal; follow-up electrolyte monitoring if QT prolongation detected

3. ERADICATION OF TUBERCULOSIS
Eradiation of tuberculosis continues to be a major health challenge for the authorities of most developing countries in the world today despite regular TB control programmes adopted by governments of these countries for the last several decades. The disease has a serious impact on the economies of these countries as it kills or debilitates people at their very productive age. Twenty two countries, including South Africa bear 80 per cent of the burden of TB worldwide. According to WHO, there are around 9 million new cases of TB detected and close to 2 million people die from the disease each year. In India, TB is rated as a major public health problem and the country accounts for one-fifth of the global TB cases. It is estimated that annually around 3,30,000 Indians die due to TB. And emergence of multidrug-resistant TB in recent years poses a much serious health threat throughout the world. In India, 12 totally drug resistant TB cases were detected at Hinduja Hospital of Mumbai early last year. Detection of these deadly TB cases seems to be rather scary especially when the world is struggling to combat the multi drug resistant TB amongst several lakhs of patients in Asia and Africa. Bedaquiline, to be sold under the brand name Sirturo by Janssen Therapeutics, a division of Janssen Products LP, was approved under the FDA's accelerated approval program on the basis of phase 2 efficacy and safety data that used the surrogate study endpoint of sputum culture conversion rather than clinical cure. The FDA had allowed the company to move forward with the phase 2 data to support its new drug application for accelerated approval because of the unmet need. However, as a condition of submission under accelerated approval, the company is obligated to conduct a confirmatory phase 3 trial. Bedaquiline is the first new TB drug since the introduction of rifampin in 1970.

4. MULTIDRUG RESISTANCE
“Multi-drug resistant tuberculosis poses a serious health threat throughout the world, and Sirturo provides much-needed treatment for patients who...don’t have other therapeutic options available,” Edward Cox, MD, MPH, director of the Office of Antimicrobial Products in the FDA's Center for Drug Evaluation and Research, said in an FDA news release. “However, because the drug also carries some significant risks, doctors should make sure they use it appropriately and only in patients who don’t have other treatment options.” A total of 440 patients with MDR-TB, defined as TB that is resistant to at least rifampin and isoniazid. In a study that was placebo-controlled, bedaquiline resulted in a significant 33% faster culture conversion within 24 weeks, with approximately 79% of those taking bedaquiline converting at 24 weeks in both the placebo-controlled and an open-label trial.

5. MECHANISM OF ACTION
Bedaquiline works via a novel mechanism of action — inhibition of a mycobacterial enzyme that is essential to the bacteria’s action — and will be indicated as part of combination therapy for the treatment of pulmonary TB caused by MDR Mycobacterium tuberculosis in adults, to be administered under directly observed therapy. Safety concerns reported by both Janssen and the FDA included signals for increased risks for QT interval prolongation, hepatotoxicity, and a greater number of deaths in the bedaquiline group compared with in the placebo group. The number of deaths was small, and at least half were deemed to be related to the TB itself, but the difference between bedaquiline and placebo (12.7% vs 2.5%) was statistically significant. The drug will carry a boxed warning alerting patients and healthcare professionals that it can affect QT prolongation. The warning also notes deaths in patients treated with bedaquiline. At the advisory committee hearing, Fred Gordin, MD, chief of infectious diseases at the Veterans Affairs Medical Center, Washington, DC, who voted yes on the efficacy but no on the safety of bedaquiline, had said he still supported the drug's approval "with the caveat that we need much more safety data... There's clearly a role for this drug, but in many patients who have other options, I think it has to be very clear to providers that there are long-term safety issues." Janssen’s phase 3 trial is planned for 2013. It is designed as a double-blind study comparing 9 months of treatment with bedaquiline with treatment with placebo, both with a background regimen.

6. CONCLUSION
India is the second country to have identified this deadly form of the disease after Iran which had some TDR TB cases four years ago. TDR-TB is caused as a result of the latest mutation of the bacilli bacteria after multi-drug-resistant TB and extremely drug-resistant TB diagnosed earlier. None of the known TB combination drugs work on patients infected by the deadly bacteria. Discovery of bedaquiline may provide a new hope for patients who are hit by the deadly disease. But as indicated by the US FDA the new drug carries some significant risks as it is still to be tried for its toxicity and effectiveness.

REFERENCES
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