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Bedaquiline

Updated: September 22, 2017.

OVERVIEW

Introduction

Bedaquiline is a diarylquinoline antimycobacterial drug used in combination with other antituberculosis medications in the treatment of multidrug resistant tuberculosis. The addition of bedaquiline to antituberculosis drug regimens has been linked to an increased rate of transient serum liver test abnormalities during treatment and to several instances of clinically apparent liver injury.

Background

Bedaquiline (bed ak' wi leen) is relatively newly approved antimycobacterial agent that has been shown to have activity against multidrug resistant mycobacterium tuberculosis both in vitro and in vivo. The mechanism of action of bedaquiline is unique: it is a diarylquinoline and is believed to act via inhibition of mycobacterial ATP synthetase; mammalian ATP synthetases not being susceptible. Bedaquiline was approved for use in pulmonary, multidrug resistant tuberculosis in combination with other antituberculosis agents in the United States in 2012 and was the first drug approved for therapy of tuberculosis is over 40 years. It is not approved for use in latent or drug sensitive tuberculosis or in atypical mycobacterial infections. In addition, bedaquiline has not been proven to be effective for extra-pulmonary tuberculosis. Bedaquiline is available in tablets of 100 mg under the brand name Sirturo. The typical dose is 400 mg once daily for 2 weeks followed by 200 mg three times weekly. Common side effects include nausea, arthralgias, headache, chest pain and rash. Bedaquiline also increases the QTc interval, but has not been linked to sudden death. On the other hand, prelicensure studies showed that patients on bedaquiline therapy had an excess mortality rate in comparison to those on placebo, a finding that has not been adequately explained and for which reason its use is restricted. Regularly updated recommendations on the use of bedaquiline and other drugs for tuberculosis, including indications, contraindications, warnings, dosages and monitoring recommendations are available at the Centers for Disease Control and Prevention website: http://www.cdc.gov/tb/publications/guidelines/Treatment.htm.

Hepatotoxicity

Liver test abnormalities occur in 8% to 12% of patients treated with multiple drug regimens that include bedaquiline. These abnormalities are usually asymptomatic, mild-to-moderate in severity and self-limited in duration. In many instances, it is difficult to determine which of the antituberculosis medications accounts for the abnormalities, but monitoring of liver tests at monthly intervals is recommended during bedaquiline therapy. Clinically apparent liver injury has been reported with bedaquiline therapy, but the clinical features, course and outcome of these cases has not been described. At least three deaths from end stage liver disease have been described in patients taking bedaquiline, but the attribution of the hepatic failure to bedaquiline has been

questioned. The management of multidrug resistant tuberculosis is challenging and should be under the direction of physicians with expertise in tuberculosis therapy.

Likelihood score: E* (unproven but suspected cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism by which bedaquiline causes serum aminotransferase elevations is not known, but is likely due to production of a toxic intermediate by its metabolism. Bedaquiline is metabolized by the liver via the P450 system (predominantly CPY 3A4) and it is susceptible to drug-drug interactions with agents that induce or inhibit CYP3A4.

Outcome and Management

Patients on bedaquiline should be monitored with monthly liver tests, including serum bilirubin, ALT, AST and alkaline phosphatase. Bedaquiline should be discontinued for persistent increases in liver test abnormalities, ALT elevations above 8 times the upper limit of normal, elevations of bilirubin more than twice normal or any symptom or sign of liver injury. There does not appear to be cross sensitivity to liver injury or adverse events between bedaquiline and other antituberculosis medications.

Drug Class: Antituberculosis Agents

Other Drugs in the Class: Capreomycin, Cycloserine, Ethambutol, Ethionamide, Isoniazid, Pyrazinamide, Rifabutin, Rifampin, Rifapentine, Streptomycin

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Bedaquiline – Sirturo®

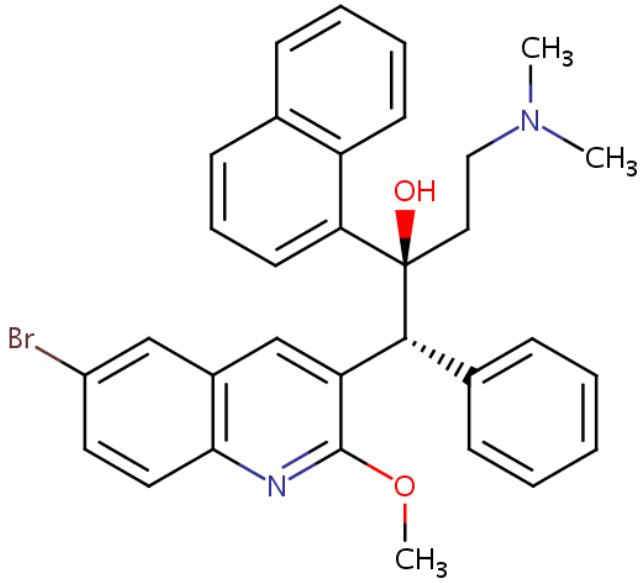
DRUG CLASS

Antituberculosis Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Bedaquiline	843663-66-1	C32-H31-Br-N2-O2	

ANNOTATED BIBLIOGRAPHY

References updated: 22 September 2017

Zimmerman HJ. Antituberculosis agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 611-21.

(Extensive review of hepatotoxicity of antituberculosis medications published in 1999 before the availability of bedaquiline).

Verma S, Kaplowitz N. Hepatotoxicity of antituberculosis drugs. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 483-504.

(Review of hepatotoxicity of antituberculosis drugs).

Gumba T. Chemotherapy of tuberculosis, mycobacterium avium complex disease and leprosy. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman.s the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1549-70.

(Textbook of pharmacology and therapeutics).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52: 2065-76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury, but none were linked to bedaquiline).

Diacon AH, Donald PR, Pym A, Grobusch M, Patientia RF, Mahanyele R, Bantubani N, et al. Randomized pilot trial of eight weeks of bedaquiline (TMC207) treatment for multidrug-resistant tuberculosis: long-term outcome, tolerability, and effect on emergence of drug resistance. Antimicrob Agents Chemother 2012; 56: 3271-6. PubMed PMID: 22391540.

(Among 47 patients with multidrug resistant tuberculosis treated with bedaquiline or placebo with background regimens for up to 6 months, major side effects not mentioned).

Centers for Disease Control and Prevention. Provisional CDC guidelines for the use and safety monitoring of bedaquiline fumarate (Sirturo) for the treatment of multidrug-resistant tuberculosis. MMWR Recomm Rep 2013 Oct 25; 62 (RR-09): 1-12. PubMed PMID: 24157696.

(Recommendations on use of bedaquiline mentions that patients should be monitored monthly and bedaquiline should be discontinued for persistent aminotransferase elevations, combined elevations of ALT or AST and bilirubin, ALT or AST elevations above 8 times the ULN, or any liver test abnormalities accompanied by symptoms of liver injury).

Chan B, Khadem TM, Brown J. A review of tuberculosis: Focus on bedaquiline. Am J Health Syst Pharm 2013; 70: 1984-94. PubMed PMID: 24173008.

(Review of the pharmacology, mechanism of action, efficacy and safety of bedaquiline mentions that liver test abnormalities were more frequent with bedaquiline than placebo [9% vs 2%], but abnormalities were transient in all except 2 patients).

Fox GJ, Menzies D. A Review of the Evidence for Using Bedaquiline (TMC207) to Treat Multi-Drug Resistant Tuberculosis. Infect Dis Ther 2013; 2: 123-44. PubMed PMID: 25134476.

(Review of the published and unpublished results of trials of bedaquiline in multidrug resistant tuberculosis mentions that two patients treated in prelicensure studies developed liver injury after being placed on bedaquiline, and died 3 months and 1 year after stopping the drug).

Chahine EB, Karaoui LR, Mansour H. Bedaquiline: a novel diarylquinoline for multidrug-resistant tuberculosis. Ann Pharmacother 2014; 48: 107-15. PubMed PMID: 24259600.

(Review of trials of bedaquiline vs placebo in multidrug resistant tuberculosis mentions that there was a statistically significant higher rate of death among bedaquiline treated patients, "the exact cause of this difference in mortality is unknown").

Kakkar AK, Dahiya N. Bedaquiline for the treatment of resistant tuberculosis: promises and pitfalls. Tuberculosis (Edinb) 2014; 94: 357-62. PubMed PMID: 24841672.

(Review of the role of bedaquiline in management of multidrug resistant tuberculosis mentions that elevated aminotransferase levels were found in 11% of bedaquiline vs 1% of placebo recipients).

Guglielmetti L, Le Dû D, Jachym M, Henry B, Martin D, Caumes E, Veziris N, et al.; MDR-TB Management Group of the French National Reference Center for Mycobacteria and the Physicians of the French MDR-TB Cohort. Compassionate use of bedaquiline for the treatment of multidrug-resistant and extensively drug-resistant tuberculosis: interim analysis of a French cohort. Clin Infect Dis 2015; 60: 188-94. PubMed PMID: 25320286.

(Retrospective analysis of 35 patients with multidrug resistant tuberculosis treated with bedaquiline mentions mild liver enzyme elevations in 5 [14%], but these were asymptomatic and transient in all, not requiring dose modification).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: the DILIN prospective study. Gastroenterology 2015; 148: 1340-52.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 408 were attributed to antimicrobial agents including 52 to antituberculosis agents, but no cases were attributed to bedaquiline).

Pym AS, Diacon AH, Tang SJ, Conradie F, Danilovits M, Chuchottaworn C, Vasilyeva I, et al; TMC207-C209 Study Group. Bedaquiline in the treatment of multidrug- and extensively drug-resistant tuberculosis. Eur Respir J 2016; 47: 564-74. PubMed PMID: 26647431.

(Among 233 adults with multidrug and extensively resistant tuberculosis treated with bedaquiline in combination with conventional agents for up to 120 weeks, sputum cultures became negative in ~70% of patients; while 5% had ALT elevations and one developed hepatitis with jaundice, there were no deaths or severe hepatic adverse events that were considered related to therapy).

Guglielmetti L, Jaspard M, Le Dû D, Lachâtre M, Marigot-Outtandy D, Bernard C, Veziris N, et al; French MDR-TB Management Group. Long-term outcome and safety of prolonged bedaquiline treatment for multidrug-resistant tuberculosis. Eur Respir J 2017; 49. pii: 1601799. PubMed PMID: 28182570.

(Among 45 adults with multidrug-resistant tuberculosis treated with bedaquiline in combination with conventional agents, liver enzyme elevations occurred in 38% but no patient stopped therapy for ALT elevations, had a serious liver related adverse event, or died from liver related causes).