Article

Use of Bedaquiline as A Novel Antitubercular Agent in Patient with Multidrug-Resistant Tuberculosis -A Review

Rajveer Singh[1], Ranjeet Kumar[2], Sonalal Prasad Kushwaha[2*]

[1]*School of Pharmaceutical Sciences, Jaipur National University, Jaipur, Rajasthan*

[2]*Department of Pharmacy Practice, NIMS Institute of Pharmacy, NIMS University, Jaipur*

Corresponding author: Sonalal Prasad Kushwaha, NIMS Institute of Pharmacy, NIMS University, Rajasthan, Jaipur, Email: sonalalprasad1996@gmail.com

ABSTRACT

Bedaquiline use as first novel drug which has been approved by the US Food and Drug Administration (FDA) in December 2012 for the treastment of MDR-TB. Bedaquiline is a type of novel reserved antitubercular drug belongs to diarylquinoline class. Bedaquiline acts on *Mycobacterium tuberculosis*, which is efficacious in rifampin,Isoniazidas well as other antituberculardrugsresistant by directly inhibiting ATP synthase enzyme. The aim of the study is to review the efficacy of bedaquilinein multidrug-resistant tuberculosis. A website based latest research which has been done by screening of different reputed research article journals, conference and review articles related to the use of bedaquiline in multidrug-resistant tuberculosis. In multidrug-resistant tuberculosis, bedaquiline is the most effectiveantituberculardrug as compare to other second line anti-mycobacterial agents. After reviewing the different article based on efficacy of bedaquiline, this drug is more efficacious in the patients with MDR-TB and it could improve the quality of life in MDR-TB patients.

Key words: Bedaquiline, antitubercular drug, resistance, MDR- TB, efficacy

INTRODUCTRION

Bedaquiline is a reserved antitubercular drug for the multiple drug resistance tuberculosis. Bedaquiline is more successful drug to treat the multiple drug resistance as compare to other anti-tubercular agent thatreportshasexaminedfrom the available data in conference preceding and review article related to bedaquilinedrug for the treatment of MRD-TB.[1]. Bedaquiline is a kind of anti-tubercular drug which belongs to the diarylquinoline class and this class is developed in 2005.Bedaquiline is the generic name and it first brand name is SIRTURO for the resistant developed by isoniazid, rifampicin,pyrazinamide, fluoroquinolones and other second line drugs, which recently approved by US food and drug administration for treatment of MDR-TB in 2012[2].Whe the treatment of multidrug-resistant tuberculosis (MDR-TB) is prolonged, by second-line drugs that are less effective and more toxic to patients than first-line drugs (Matteelliet al., 2007). Thus, treatment outcomes are undesirable. According to global MDR-TB cohort completed successful treatment only 54 % of patients in a 2014 (World Health Organization, 2017).

Which effective drugs for the treatment of MDR-TB are lacking. Bedaquiline is inhibits mycobacterial ATP synthase, which has been introduced recently clinically.[3]Any person is suffering from MDR tuberculosis than that time mostly resistant developed with isoniazid and rifampicin its means this drugs do not work against bacteria[4].Bedaquiline one type of fumarate substance which is aalmost white powder and it is practically insoluble in aqueous solvent. It has a molecular formula of C32H31BrN2O2 · C4H4O4 and a molecular weight of 671.58 (555.50 + 116.07)[5].

According to Janssen Pharmaceuticalscurrently cost of bedaquilinearound $136 per month ($820 for a six-month course that announced by the South African government) for bedaquilinIn 2014, and in the 2015 march announced the price structure of bedaquiline $900, $3 000 or $30 000 for a six-month course, this depending on the economic condition of the country[6].

According to current studies their are limited clinical data available to evaluatebedaquiline safety and effectiveness for the treatment of MDR-TB that is by the demand of bedaquiline in the market rising day by day[1]. Bedaquiline is responsible to inhibit an adenosine triphosphate (ATP)syntheses enzyme. When the treatment of MDR-TB by the bedaquilinethan nausea is more appeared and it increases the QT interval.It is not recommended for <18 year children, pregnant and lactatlingwomen,all these reports are available on the related to the drug review article in PUBMED[7].

The causative agent of TB that is *Mycobacterium tuberculosis*. It is a kind of pathogenic bacteria which belong from Mycobacteriaceae family. This family contains the single genome mycobacterium with over 150 species[8]. This bacteria is aerobic species that is why high amount of oxygen require for the growth and development of the cell and this types of the bacterial growth more in the acid fast environment. This disease is transmitted by person to person through air.

There are about 10 million people are infected by TB world wideand according to WHO data 1.6 million died from this disease each year (including 0.3 million along people with HIV)[9].

Bedaquiline was recently approved for the treatment of MDR-TB. This report is available on different preceding and review article related to bedaquiline treatment in tuberculosis resistance.

According to report of the US food and drug administration, standard treatment regimens are always highly effective for patient required sensitive combination of four drug for two month and whereas two drugs for 2-4 month. however, patient condition day by day treatment outcome are substantially worsening for patient with disease that resistant to isoniazid and rifampicin. This condition is appeareddue to irregular or absence of direct observe therapy (DOT) program awareness and due to absence of knowledge of drug cause the worsen condition of the patient[(1)].

Some time treatment of MDR-TB is substantially a lot of complex treatment, costly and less effective than standard treatment or therapy with at least 6 anti-tubercular agents. (including an injectable for more than 18 month.)

Extensively drug resistance XDR is defined as the fluoroquinolones and second line drugs.

When the prolong treatment by the injectable fluoroquinilones and 2ND line drugs that is called XDR. This drug is treated to both MDR-TB or XDR-TB. After often poor tolerated due to adverse effect the successful case is only 50-70% MDR and not less than 40% case XDR TB. After that the limitation of the therapy stop and addition of high quality of regimens are develop that should be more effective against drug resistance disease.

Bedaquiline (previously known as TMC-207) is diarylquinolines class of TB antibiotic. Before approved more clinical and preclinical study about bedaquiline, this drug is approved by US food and drug administration for the used treatment of pulmonary MRD-TB in 2012 and according to WHO is also recommended for the treatment of pulmonary MRD-TB and after that purchase of bedaquilinein the market day by day rises because this drug is more safety and effectiveness as compare to other anti-tubercular agent.

A web based research has been done screening of the various research articles, conference preceding and the website of the US FDA was also search was perform using PUBMED and review article related to bedaquiline treatment in tuberculosis resistance[(1)].

Bedaquiline is well absorbed orally, fatty meal improve absorption. It is highly plasma protein bound and extensively distributed in tissue. Metabolism occurs in liver, mainly by CYP3A4, and it is excreted mainly in faeces. According to WHO in 2013 issued guidelines of bedaquiline for how to use of bedaquilinein drug resistant TB, following the RNTCP 2016 has introduce BDQ in India for MDR–TB at selected centers through it conditional access program.

Now present recommended regarding use of BDQ:

- It should be used only for pulmonary MDR-TB in adult (>18Yr) but not used in (<18 yr)
- When women use than women should be non-pregnant
- It should be used only combination with at least 3 other anti –TB drugs to which the bacilli of the patients are show to be susceptible in vitro, or at least 4 other drugs to which the patients isolate is likely to be sensitive.

Bedaquiline (BDQ) should be given for maximum of 24 weeks in which the dose of 400 mg/day for starting 2 weeks after that the dose of 200mg 3 time a week for next 22 weeks

Bedaquiline is not used for drug –sensitive TB, or extrapulmonary TB or fornontubercular mycobacteria.

Adverse effect of BDQ are nausea, headache, arthralgia and prolongation of QT interval[9].

MECHANISM

Bedaquiline is specially target to inhibit mycobacterial adenosine triphosphates (ATP) syntheses that enzyme are more responsible for the generation of energy and provides energy to M. tuberculosis and it has bactericidalproperties. This drug is structurally and mechanistically different fromfluoroquinolone antibiotics and other than quinolones class of drugs. It means that fluoroquinolonesis also used in the treatment of MDR-TB[9].

Fluoroquinolones act on both bacteria like gram positive and gram negative. The mechanism of action of fluroquinolones are:

In case of gram negative bacteria

- Fluoroquinolones inhibit bacterial DNA gyrase enzyme which necessary to cut the double stand DNA, introduce negative supercoil and then reseal the cut end, this necessary to prevent excessive positive supercoiling of strains. When they separate to permit replication or transcription
- DNA gyrase consist of two sub units A and B unit, A subunit carried out necking of DNA, whereas B subunits introduce negative supercoil and A subunit with high affinity and interfered with its strain cutting and resealing function.

In case of gram positive bacteria

- In gram positive bacteria fluoroquinolones act on topoisomerase IV enzyme which is required to cut and separate to daughter DNA strains after replication.
- Bactericidal action probably result from digestion of DNA by exonucleases.

Topoisomerase II enzymes are present in the human body but drugs does not effect on this enzymes if the dose of drug increased than it may shows effect on this enzymes and cause cytotoxicity [10]

RESULT & DISCUSSION

Bedaquiline is the most effective against *Mycobacterium tuberculosis* as compare to the other anti-mycobacterial agents like flurouquinolones and 2nd line drugs because 2nd line drugs are used for prolong time more than 18 month. Sometimes patient has not taken drug properly day by day due to some reasons like complex treatment, high costly drugs, less effective than standard therapy that is whybedaquilinewhich have the short duration treatment that are more effective than other anti-tubercular agents.

CONCLUSION

After reviewing the different article based on efficacy of bedaquiline, it observed that this drug is more effective in the patients with MDR-TB and it could improve the health back ground MDR-TB patients.

When the patients taking treatment with Bedaquiline for short duration as compare to other anti- tubercular drugs so it provide more support and protect to the health and economic factor as compare to other antitubercular drugs.

CONFLICT OF INTEREST

Authors don't have any conflict of interest

REFERENCES

1. GregoryJ.Fox, DickMdenzies.A Review of the Evidence for Using Bedaquiline (TMC207) to Treat Multi-Drug Resistant Tuberculosis. Springerlink. 2013; 2(2):123-144.
2. TBElimination Treatment of Multidrug-Resistant Tuberculosis: Bedaquiline. Available on http://www.cdc.gov/tb, last visited on 4th March, 2019.
3. Seyeon Park, Kyu Min Lee, Insu Kim, JeonghaMok. The use of bedaquiline to treat patients with multi drug resistant tuberculosis and end-stage renal disease: A case report. International journal of infectious diseases. 2018; 76:88-90.
4. Bedaquiline - What is it? dose, trials, side effects, cost, South Africa. Available on https://www.tbfacts.org/bedaquiline/, last visited on 4th March, 2019.
5. Activists call on Johnson& Johnson to drop the price of Bedaquiline. Available on http://tbonline.info/posts/2018/7/13/activists-call-johnson-johnson-drop-price-bedaquil/, last visited on 3rd March, 2019.
6. Field K. Stephen. Bedaquiline for the treatment of multidrugresistant tuberculosis: great promise or disappointment? SAGE Journals. 2015; 6(4): 170-184.
7. Jean Paul Assam Assam, Veronique PenlapBeng and Vincent P K Titanji. Mycobacterium tuberculosis is the causative agent of tuberculosis in the southern ecological zones of Cameroon, as shown by genetic analysis. BMC Infect Dis.2013; 13:431.
8. Available onhttps://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death, last visited on 3rd March, 2019.
9. Tripathi KD. Essential of Medical Pharmacology. 8th edition. New Delhi.Jaypee Brothers Medical Publishers (P) LTD; 2018.
10. David C. Hooper. Mechanisms of action and resistance of older and newer fluoroquinolones. Infectious Disease Society of America. 2000; 31(2): S24-S28.

Received: 15 Feb, 2021, Decision for Acceptance: 27 Mar, 2021

Cite this article

RajveerSingh, Ranjeet Kumar, Sonalal Prasad Kushwaha. Biopharmaceutics Classification System (BCS) and Biopharmaceutics Drug Disposition Classification System (BDDCS) – An Approach for Drug Development and Advancement, Indian Journal of Healthcare, Medical & Pharmacy Practice. 2021; 2(1):25-28