Impact of Bedaquiline on Multidrug-Resistant Tuberculosis Treatment to Mother and Baby: An Incidental Case

Tutik Kusmiati[1], Faradila Nur Aini[2]

[1]Medical Staff, Infection Division, Departement of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Airlangga – Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, [2] Resident, Departement of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Airlangga – Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

Abstract

Background: Bedaquiline is a new drug which is recommended by World Health Organization (WHO) for individual regiment drug resistant-tuberculosis (DR-TB). The presence of regiment DR-TB in the blood is long enough with $T^{1/2}$ 5-6 months, that is why bedaquiline is given on six months. Bedaquiline is not recommended for pregnant women because there is no data related to safety. The author will report an incidental pregnant female on bedaquiline treatment.

Case presentation: A 24-year-old woman with multidrug resistant tuberculosis (MDR TB) on individual regiment bedaquiline had incidental pregnancy at the 6th month treatment. In the beginning, the patient used bedaquiline because of the intolerance of second-line injectable drug. Bedaquiline regiment was used for 24th week. Pregnancy occured at the 6th month treatment. The patient continued the pregnancy and the MDR TB treatment was continued without bedaquiline. Nausea and vomiting were getting worse. Preterm labour occured in 33/34 weeks by cesarean section. The baby had severe asphyxia, used continuous positive airway pressure (CPAP), treated in NICU, had low weight but there was no disability. After several days of treatment, the condition of baby was improving and was able to outpatient.

Conclusion: The preterm labour, low birth weight, and neonatal emergency occured in a pregnant woman with MDR TB on individual regiment bedaquiline. Mother and baby can survive. More case and research data are needed on the safety of bedaquiline during pregnancy.

Keywords: *bedaquiline, multidrug resistant tuberculosis, pregnancy, mother, baby*

Introduction

Treatment of multidrug resistant tuberculosis (MDR TB) is increasingly complicated when the patient is pregnant. Pregnancy can occur when a patient has been diagnosed with MDR TB and is undergoing treatment or the pregnant woman diagnosed with MDR TB. There are still some controversial opinions regarding the management of MDR TB with pregnancy [(1)]. Some clinicians recommend terminating pregnancies and continuing MDR treatment. Other clinicians delay administration of the drug temporarily, especially in the early trimester. This doubt occurs because there is no data on the safety of MDR TB drugs in pregnant women and fetuses.

Corresponding outhor:
Tutik Kusmiati
Infection Division, Departement of Pulmonology and Respiratory Medicine, Faculty of Medicine, Universitas Airlangga – Dr. Soetomo General Academic Hospital, Jalan Mayjen Prof. Dr. Moetopo 6 – 8, Airlangga, Gubeng, Surabaya 60286, Indonesia
Mail: tut.kusmiati@gmail.com
Phone: +6231-5501656
ORCID ID: 0000-0002-5686-2377

Case Presentation

A 24-year-old woman with MDR TB on individual regiment bedaquiline had incidental pregnancy at

the 6th month treatment. In the beginning, Acid-Fast Bacillus (AFB) sputum was positive, GeneXpert was *Mycobacterium tuberculosis* detected very low, Rifampicin Resistance detected, drug susceptibility testing (DST) was resistant of Rifampicin, Isoniazid, Ethambutol, Streptomycin, and sensitive of Kananycin, Ofloxacin, Amikacin. The patient had moderate depressive episodes without psychotic symptoms because she had received TB treatment for the third time and treatment of MDR TB which took longer. Electrocardiography was within normal limit and there was no elongation of corrected QT interval (477 ms QTc). There was mild hearing loss on the right ear based. The laboratory data was normal. The patient had a strong motivation for treatment and recovery.

Before Pregnant: The patient used individual regiment bedaquiline because of intolerance of second-line injection drugs. Bedaquiline regiment was used for 24th week. The regiment was Pyrazinamida 1000 mg / Levofloxacin 750 mg / Ethionamide 500 mg / Cycloserine 500mg / Para-amino salicylic acid 8 mg / B6 100 mg with Bedaquiline 400 mg every day in the initial 2 weeks, and then continued with bedaquline 200 mg three times a week. The patient had nausea and vomiting but medication was taken regularly.

Pregnant: Pregnancy occurred at the 6th month treatment. The patient continued the pregnancy and MDR treatment was continued without bedaquiline. The regiment was Pyrazinamida 1000 mg / Levofloxacin 750 mg / Ethionamide 500 mg / Cycloserine 500 mg / Para-amino salicylic acid 8 mg / B6 100 mg. Nausea and vomiting were getting worse and she had lost 5 kg of weight the first month of pregnancy. The patient had routine control of the pregnancy. There were no serious complaints during Antenatal Care.

Labour: Preterm labour occurred in 33/34 weeks gestation. Pregnancy had been maintained by tocolytic but it was unsuccessful. The bullae in both lung fields patient should the patients had sectio caesaria surgery and cannot vaginam labour (figure 1). There was no complication such as bleeding on the mother during operation process. The baby was female with clear coloured membranes but the baby had severe asphyxia (Apgar Score 3) in the first minute and was getting increase at the next evaluation. The baby used continuous positive airway pressure (CPAP) and treated in Neonatal Intensive Care Unit (NICU) for several days. Her weight was 1,950 gram so classified as low birth weight (LBW) but there was no disability. Babygram was within normal limit (figure 2). After several days of treatment, the baby was getting improved and transferred to the baby care room, which was then allowed to outpatient.

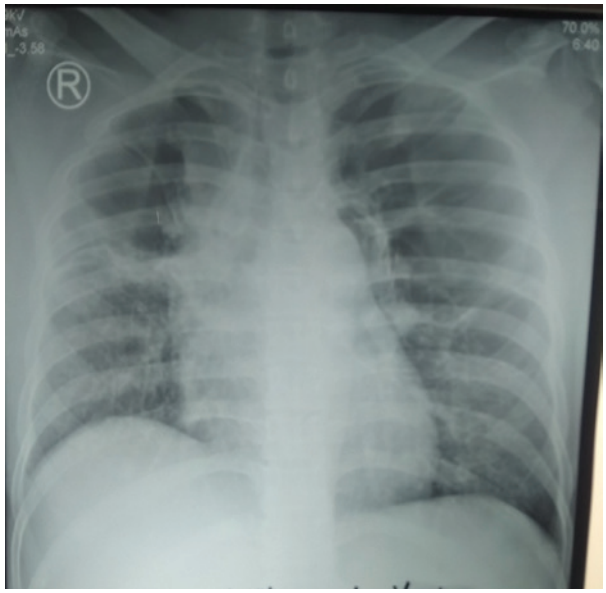

Figure 1. Chest X-ray revealed the fibrotic process and multiple bullae in right and left apex hemithorax.

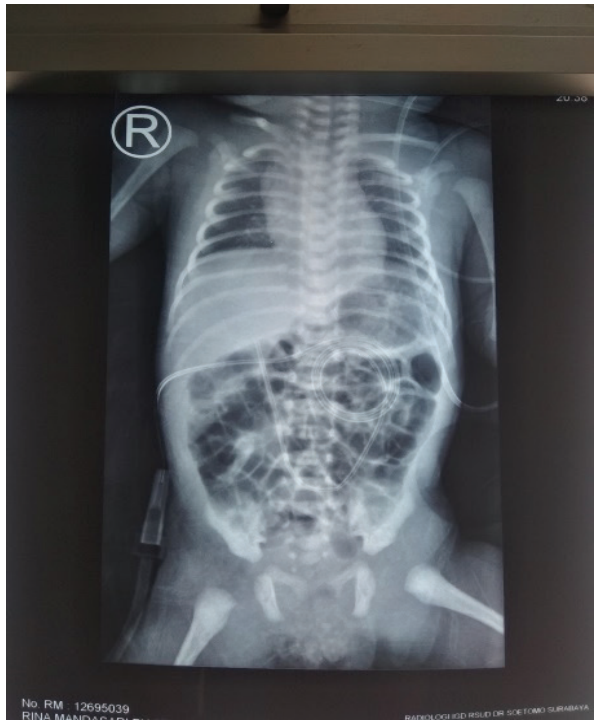

Figure 2. Babygram.

Discussions

Pregnant women with untreated TB have morbidity, the risk of vertical transmission, and mortality rate of 40% [2]. There is an increased risk of pregnancy complications such as spontaneous abortion, oligohydramnios, preterm labour, Intra Uterine Growth Restriction (IUGR), Intrauterine fetal Death (IUFD), and an increased risk of neonatal death. Therefore, pregnant women with TB need to be treated effectively before giving birth, including women with MDR TB. However, the clinician is often doubtful about the treatment because there is no data on safety.

Bedaquiline is bactericidal which is given an additional drug for MDR TB patients. Although bedaquiline is not teratogenic, there is no data on the safety of pregnant women. In this patient, pregnancy occurs at 6th month bedaquiline treatment. Bedaquiline has already stopped but the half-life (T1/2) is still around 4-5 months [3, 4]. However, Bedaquiline is still in the blood and passes through the placenta to the fetus. This can impact the pregnancy in the first and second trimester.

Although bedaquiline was declared not teratogenic and mutagenic in the in vivo and in vitro studies, there was no study in pregnant women [1, 5, 6]. In this patient, Partus Premature Imminent (PPI) occurs at 33/34 weeks of gestation by cesarean section. The baby had severe asphyxia with Apgar Score 3, but with good treatment, the Apgar score was increased in the next evaluation. The baby used CPAP and treated in NICU. Baby had low weight but there was no disability. After several days of treatment, the baby condition was improving and was able to outpatient.

Transmission of TB from mother to baby can occur during the fetus or after childbirth. TB in the fetus can occur when there is spread through the placenta during pregnancy. But this congenital tuberculosis is rare. In this situation, *Mycobacterium tuberculosis* has been identified in the amnion, decidua, and chorionic villi [7, 8]. But this rarely happens if the mother has undergone effective treatment in pregnancy. In this patient, there is no specific process in umbilical histology examination. This is in accordance with the theory because mothers have received TB treatment well.

Conclusion

The preterm labour, low birth weight, and neonatal emergency occur in a pregnant woman with MDR TB on individual regiment bedaquiline. Mother and baby can survive. However, further monitoring is needed regarding the possibility of transmission of TB after birth. More case and research data are also needed on the safety of bedaquiline during pregnancy.

Ethics Statement

All procedures performed in studies / case report were in accordance with the ethical standards of the Ethics Committee in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. The authors explains the aimed, benefits, and rights of the participant during the process of collecting data to the patient's guardian, if the participant agrees we ask the participant to fill out an informed consent sheet.

Conflict of Interest: The authors report no conflict of interest in this publish.

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References

1. Drobac PC, del Castillo H, Sweetland A, Anca G, Joseph JK, Furin J, et al. Treatment of Multidrug-Resistant Tuberculosis during Pregnancy: Long-Term Follow-Up of 6 Children with Intrauterine Exposure to Second-Line Agents. Clinical Infectious Diseases. 2005;40(11):1689-92.
2. Jaspard M, Elefant-Amoura E, Melonio I, De Montgolfier I, Veziris N, Caumes E. Bedaquiline and Linezolid for Extensively Drug-Resistant Tuberculosis in Pregnant Woman. Emerg Infect Dis. 2017;23(10):1731-2.
3. Chahine EB, Karaoui LR, Mansour H. Bedaquiline:A Novel Diarylquinoline for Multidrug-Resistant Tuberculosis. Annals of Pharmacotherapy. 2014;48(1):107-15.
4. Worley MV, Estrada SJ. Bedaquiline: A Novel Antitubercular Agent for the Treatment of Multidrug-

Resistant Tuberculosis. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2014;34(11):1187-97.

5. Shin S, Guerra D, Rich M, Seung KJ, Mukherjee J, Joseph K, et al. Treatment of Multidrug-Resistant Tuberculosis during Pregnancy: A Report of 7 Cases. Clinical Infectious Diseases. 2003;36(8):996-1003.
6. Palacios E, Dallman R, Muñoz M, Hurtado R, Chalco K, Guerra D, et al. Drug-Resistant Tuberculosis and Pregnancy: Treatment Outcomes of 38 Cases in Lima, Peru. Clinical Infectious Diseases. 2009;48(10):1413-9.
7. Ormerod P. Tuberculosis in pregnancy and the puerperium. Thorax. 2001;56(6):494-9.
8. Loto OM, Awowole I. Tuberculosis in pregnancy: a review. Journal of pregnancy. 2012;2012.