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Case Report

Use of Bedaquiline as a Replacement for Aminoglycosides in the MDR-TB Regimen and the Risk of Acquired Resistance: a Case Report

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ABSTRACT

This case report highlights the difficult management of recurrent multidrug-resistant tuberculosis without cultures and using only new molecular methods as the decision-making tools in low-income countries such as the Democratic Republic of the Congo. This paper highlights the relevance of solid or liquid medium culture and all drug susceptibility testing in choosing an appropriate therapeutic regimen and questions the new WHO TB guidelines recommending the use of bedaquiline to replace injectable drugs.

Introduction

The Democratic Republic of Congo (DRC) has an estimated population of 81 million and a tuberculosis (TB) incidence rate for all forms of TB of 262 cases per 100,000 inhabitants [1]. The DRC is one of the 22 countries that support more than 80% of the global burden of TB and ranks third in Africa. The estimated prevalence of rifampicin-resistant TB is 2.2% among new cases and 9.6% in previously treated TB [1,2]. The DRC has difficulty with the bacteriologic follow-up (drug susceptibility test with the culture method) during MDR TB management; the gap in the diagnosis of MDR/RR TB cases was 74% in 2017 [1], and the impact of fluoroquinolone resistance (FQ R) is not known. In an observational study in 9 African countries, Trébucq et al. [2] Reported a 4, 7% FQ R rate. This is a major problem for the National Tuberculosis Program.

In the new TB guidelines, if there is no FQR, bedaquiline is recommended to replace injectable drugs in MDR TB regimens to prevent hearing loss [3]. However, the DRC is a disadvantaged low-income country. There are no phenotypic drug susceptibility tests available in any center; the line probe assay (LPA) for first-line drug (FLD) susceptibility and second-line drug (SLD) susceptibility are available only at the central level. This deficiency can result in administering bedaquiline to patients with FQ R and may lead to early acquired resistance.

We present the case of a patient who received a modified short tuberculosis treatment and developed probable acquired resistance.

Case Study

A 25-year-old woman receiving tuberculosis treatments

had one long MDR TB treatment in 2015. Over 24 months, she received levofloxacine (LFX), cycloserine (Cs), ethambutol (E), and pyrazinamide (Z) and was supplemented during the minimum 6-month intensive phase by KM and prothionamide (PTM) (6 KM-LFX-PTM-Cs-E-Z + 18 LFX-PTM-Cs-E-Z). She also had supraventricular tachycardia. After this TB regimen, she was cured.

Six months after that TB regimen, she complained of fever, weight loss, cough, left chest pain, dysphagia and hearing impairment. The sputum smear was once again positive (3 cross). The GenXpert test (Cepheid, USA) showed rifampicin resistance, and the Hain test (GenoTypeMTBDRsl, HainLifescience) found susceptibility to fluoroquinolone and injectable drugs.

Physical examination revealed a patient with pallor, a body mass index of 15,77 kg/m^2, a heart rate of 132/min, a respiratory rate of 30/min, a blood pressure of 100/60 mmHg, and an axillary temperature of 38°C. Crackles were found in the right upper half of the lung along with a cavitary sign in the left lung and incomplete cardiac arrhythmia. No abnormality was found on abdominal examination; there was no digital clubbing and no edema. Direct microscopy showed AFB positivity (2 cross). Audiometry showed mild deafness. Relapsing MDR TB was diagnosed.

It was decided that the patient would receive the short TB regimen for MDR TB with one modification: bedaquiline replaced the kanamycin to prevent aggravation of the hearing impairment. The patient received 6 months of bedaquiline (4 tablets for 2 weeks, then 2 tablets three times a week for 22 weeks) and 4 months with Levofloxacine (LFX),Prothionamide (PTM), Clofazimine (Cfz), high-dose Isioniazide (hINH), Ethambutol (E), and Pyrazinamide (Z) in the intensive phase, followed by 5 months of only LFX, Clz, E, and Z in the continuation phase.

Bdq	LFX	PTM	Cfz	hINH	E	Z
2x200 mg (14 days), 200 mg 22 weeks	750 mg	500 mg	100 mg	300 mg	600 mg	800 mg

During this modified short TB regimen, the smears were negative from the second month to the 7th month (Table 1). The major side effect was QTc prolongation after 5 months of treatment; bedaquiline was stopped (Table 2). Sputum culture controls were not available during treatment or were returned contaminated. Only smear microscospy (two specimens monthly) was used during the follow-up. At the 8th month of treatment, the sputum smear returned positive (3 cross). Failure of the modified short MDR TB regimen containing bedaquiline was suspected. LPA FLD and SLD were again performed and showed rifampicin resistance, high-level INH resistance, injectable drug susceptibility, and acquired FQ resistance (gyrA MUT3A).

Discussion

This case highlights the need for fluoroquinolone sensitivity before modifying a short TB regimen [2,4]. If the patient has a previous history of using FQ, the use of a high dose would have been needed. Bedaquiline use must be reserved by first using another drug with early bactericidal activity, such as linezolid or delamanid [5-7].

When LPA shows FQ susceptibility in patients with a previous exposure to FQ, it is likely a case of missed FQ heteroresistance [8]. This is also explained by the limit of detection of the LPA for second-line drugs, which is 5%; below this threshold, the test may be falsely negative.

Table 1: Bacteriological follow-up to the smear and culture.

Date	Sputum Smear microscopy	Culture
Month 0	++	Not available
Month 1	+	Not available
Month 2	Negative	Contaminated
Month 3	Negative	Not available
Month 4	Negative	Negative
Month 5	Negative	Not available
Month 6	Negative	Contaminated
Month 7	Negative	Not available
Month 8	+++	Not available

Table 2: Side effects during treatment.

	M1	M2	M3	M4-5	M7
Clinical	apyrexia	weight gain			Fever Malaria
	Vomiting Arthralgia Gastritis Anemia: Blood transfusion	None	Severe tachycardia ECG: 150-220 bpm Supraventricular tachycardia: betablockers	QTc prolongation 5th M 15 days QTc 500 ms Bedaquiline was stopped	

The use of several antibiotics, which are very important in the TB regimen, will create a selective pressure for resistant mutants and promote FQ mutant resistance as in this case. Rigouts et al. [9] had the same result in their study. The consequence will be the occurrence of acquired bedaquiline (Bdq) resistance. Therefore, the use of Bdq as a core drug in the first TB regimen is not good [3,6,7,10]. The result is the failure shown by the fall and rise phenomenon [9]. This was the case here.

Many authors have also mentioned the cross resistance between clofazimine and bedaquiline [11]. The resistance to Bedaquiline can expose Clofazimine activity; this patient, despite the long exposure to FQ, she received FQ at a normal dose. She developed high-level INH resistance and had cross-resistance with prothionamide with a poor prognosis, as described in the literature [6,12].

Acquired resistance to FQ exposed this patient to bedaquiline resistance, and the whole therapeutic regimen was thus compromised, explaining the failure.

Conclusions

The management of MDR TB patients in countries where culture facilities are limited is hard. Repeated LPA is not a suitable alternative to cultures. The genotypic diagnostics totally replacing the phenotypic solid and liquid diagnostics and the hurried manner in which Bedaquiline found a way up in the treatment as second line drug are the two draw backs influencing TB treatment. This case report brought out the grey area due to lack of phenotypic DST facility especially in developing countries where MDR TB patients are treated with Bedaquiline leading to Fluoroquinolone Resistance.

Conflicts of Interest

Authors declares that there is no conflict of interest regarding the publication of this paper

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