Treatment outcomes of patients switching from an injectable drug to bedaquiline during short standardized MDR-TB treatment in Mozambique

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Abstract

Bedaquiline was recommended by WHO as the preferred option in treatment of MDR-TB patients with long regimen. However, no recommendation was given for the short MDR-TB regimen. Data from our small cohort of patients who switched injectable dug to bedaquiline suggest that bedaquiline based short regimen is effective and safe.

Introduction

Short standardized treatment for multidrug-resistant Tuberculosis (MDR-TB) has been recommended by the World Health Organization (WHO) since 2016 for patients not previously treated with second-line agents and without second-line resistance [1,2]. However a significant proportion of patients experience numerous severe adverse events linked to the use of second-line injectable drugs including ototoxicity, nephrotoxicity and electrolyte imbalance, which could lead to discontinuation of treatment or to permanent physical injury to patients [3].

In 2018, WHO revised its recommendations about MDR-TB treatment regimens [4]. The use of kanamycin and capreomycin are no longer recommended in the long regimen and bedaquiline is preferred. However, due to lack of evidence, bedaquiline is not recommended for the short regimen and the only modification is a recommendation to replace kanamycin with amikacin. WHO encourages field evaluation of modified shorter MDR-TB regimens including bedaquiline instead of injectable drugs.

In 2015, MSF launched a prospective study to describe the efficacy of the short MDR-TB regimen in Maputo, Mozambique. Patients who experienced adverse events which could be attributed to one specific drug could remain on the short MDR-TB regimen with the causative agent replaced by bedaquiline.

In this paper, we report the outcomes of patients started on a short standardized MDR-TB regimen in whom the injectable drug was replaced with bedaquiline due to adverse events.

Methods

Beginning in 2015, we have conducted a prospective longitudinal study in Maputo, Mozambique where MSF provides support to the Ministry of Health for DR-TB. The study population consisted of

all patients with active pulmonary tuberculosis diagnosed as rifampicin resistant by Xpert or phenotypic drug susceptibility testing (DST). Patients resistant to fluoroquinolones alone or to fluoroquinolones and injectables were excluded from the study. Patients resistant to injectable agents (Kanamycin and Capreomycin) will continue the short regimen if, once the DST results are available, their clinical condition has improved compared to baseline. If the clinical condition is worsening or remains the same they will be withdrawn from the study and switched to a more appropriate regimen. Additional resistance to a drug of the regimen was not a criteria for exclusion.

The regimen consisted of an intensive phase with Pyrazinamide/Ethambutol/Isoniazid/Moxifloxacin/Kanamycin/Prothionamide/Clofazimine for at least 4 months and a continuation phase with Pyrazinamide/Ethambutol/Moxifloxacin/Prothionamide/Clofazimine for fixed 5 month duration. Patients could continue with a short regimen with bedaquiline in the following cases: Grade 2 and above ototoxicity associated with kanamycin, grade 3 and above nephrotoxicity associated with kanamycin and grade 3 and above gastrointestinal disorders associated with Prothionamide. In such cases, the causative drug was stopped and replaced by bedaquiline at standard dosage for 6 months. Culture and DST were performed in the Institute of Tropical Medicine (ITM) in Antwerp, Belgium. Patients were eligible for this analysis if they started short MDR-TB treatment and if kanamycin was replaced by bedaquiline due to adverse events. Database censoring was on the 31st August 2018.

We described the characteristics of eligible patients and the reasons and timing of switching from kanamycin to bedaquiline. MDR-TB treatment outcomes were defined per WHO definitions: cured (treatment completed without evidence of failure and three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase), treatment completed (treatment completed without evidence of failure but no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase), death, treatment failure and lost to follow-up [5]. Culture conversion was defined as two consecutive negative cultures more than 28 days apart. Adverse events were assessed according to the Division of AIDS (DAIDS) grading score. Analyses were performed with Stata 15 (Stata Corporation, College Station, Texas, USA).

This study was approved by the Ethical Review Board of Médecins Sans Frontières, the Ethical Review Board of ITM Belgium and the Ethical Review Board of Mozambique. All treatment was

provided free of charge irrespective of participation in the study. Participation was voluntary after written informed consent.

Results

A total of 164 patients starting a short MDR-TB treatment regimen were included between November 2015 and May 2018. Among them, 19 (11.6%) switched from kanamycin to bedaquiline due to adverse events. The main reason to stop kanamycin was ototoxicity (17/19 (89.5%)); one patient experienced nephrotoxicity and another hypokalemia.

Characteristics of these patients are presented in Table 1: 57.9% were males, median age was 35 [IQR 26-48], median BMI was 17.6 kg/m² [IQR 15.8-19.9] and 63.2% were HIV-positive. Among them, 14 (73.7%) were new TB cases, 4 (21.0%) were previously treated with first line drugs and were relapse and 1 (5.3%) was previously treated with first list drug and failed previous treatment. At treatment initiation, 14/19 (73.7%) were culture positive and the DST showed that 6 (31.6%) were resistant to Streptomycin, 7 (36.8%) were resistant to Ethambutol, 7 (36.8%) were resistant to Pyrazinamide, 7 (36.8%) were resistant to Ethionamide. No patients were resistant to fluoroquinolones or injectable drugs. In total, 7 (36.8%) of the patients were resistant to more than 1 drug among the previous drugs listed, and 6 (31.6%) were resistant to more than 2 drugs.

The median time from treatment start to switching kanamycin to bedaquiline was 2.76 months [IQR 2.20-3.61] and the median duration of treatment with bedaquiline was 24 weeks [IQR 24 – 26] after switch.

Among the 16 patients that started the short MDR-TB regimen before 1st October 2017 (11 months prior to censoring date), 13/16 (81.3%) were cured and 3/16 (18.7%) completed treatment. Taken together, we observed 100% treatment success among patients that switched kanamycin to bedaquiline. Among the other 3 patients still on treatment, 3 (100%) already converted culture in the first 4 months of treatment.

All 5 patients that were culture negative at treatment start remained culture negative during the whole treatment length. Among the 14 patients who were culture positive at treatment start, 9 were already culture negative at bedaquiline start and 5 were still positive when bedaquiline was started.

No grade 3 or 4 QT prolongation and AST/ALT increase were observed on monthly ECG's during the time that patients received bedaquiline.

Discussion

Among our small cohort of 19 patients, we observed a high proportion of favorable outcomes and no major safety issues among those switched from an injectable to bedaquiline on a short MDR-TB regimen in Mozambique.

At bedaquiline initiation, most patients were already culture negative, which limits the interpretation about efficacy of bedaquiline. In addition at the time of analysis, post-treatment assessment 12 months after end treatment has been yet done, though it is not possible to conclude about relapse rate. However, toxicity of injectable agents is extremely common during MDR-TB treatment and is a major concern for the success of MDR-TB treatment [3]. The proportion of patients who experienced hearing loss or other ototoxicity (potentially eligible for switching from injectable drug to bedaquiline) might be even higher than in this study since some patients might die before developing ototoxicity. At the same time, no evidence of major safety issues with bedaquiline were demonstrated; QT interval prolongation is known to be associated with bedaquiline but very few episodes are of clinical relevance [6,7]. These episodes could be handled safely with temporary interruption of cardio toxic drugs together with a regular monitoring of ECG [8]. Recent studies have already shown the efficacy of bedaquiline among patients resistant to second-line drugs using a long MDR-TB treatment regimen [9–12].

Many programs are considering implementation of all-oral short regimen. While more data on a short regimen with bedaquiline are needed, we believe that data from our small cohort suggest that bedaquiline based short standardized regimen is effective and safe, and that patients who

developed ototoxicity including hearing loss during short MDR-TB regimen may continue with short MDR-TB with replacing the injectable agent with bedaquiline and not switch to longer MDR-TB treatment.

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Table 1 - Characteristics and outcomes of the 19 patients that switched kanamycin to bedaquiline during short MDR-TB regimen in Mozambique

Characteristics	**N (%)**
Gender	
Male	11 (57.9)
Female	8 (42.1)
Age (years)	
Median [IQR]	35 [26-48]
BMI (kg/m²)	
Median [IQR]	17.6 [15.8-19.9]
HIV	
Negative	7 (36.8)
Positive	12 (63.2)
On-ART at MDRTB treatment start Receive ART at MDRTB treatment start	7 (58.3) 5 (41.7)
Antiretroviral therapy	
TDF/3TC/EFV	5 (41.7)
AZT/3TC/EFV	3 (25.0)
ABC/3TC/EFV	2 (16.7)

ABC/3TC/NVP	1 (8.3)
AZT/3TC/Lpv/r	1 (8.3)
TB treatment history	
New case	14 (73.7)
Previously treated with first line drugs (relapse)	4 (21.0)
Previously treated with first line drugs (treatment failure)	1 (5.3)
Culture results	
Negative for MTB*	5 (26.3)
Positive for MTB	14 (73.7)
DST results	
Streptomycin resistance	6 (31.6)
Ethambutol resistance	7 (36.8)
Pyrazinamide resistance	7 (36.8)
Ethionamide resistance	7 (36.8)
Injectable resistance	0 (0.0)
Fluoroquinolone resistance	0 (0.0)
Resistance to > 1 drug	7 (36.8)

Resistance to > 2 drugs	6 (31.6)
Treatment outcomes	**N=16**
Cured	13 (81.3)
Treatment completed	3 (18.7)
Death	0
Failure	0
Lost to follow-up	0
Still on treatment	**N=3**
Culture conversion	3 (100)

*MTB = *Mycobacterium tuberculosis*