Original Article

Safety of Antituberculosis Agents used for Multidrug-Resistant Tuberculosis among Patients Attending the Jamot Hospital of Yaounde, Cameroon

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Abstract

Background: Recognized in 1994 as a global emergency by the World Health Organization, tuberculosis (TB) remains an ongoing health threat. In Cameroon, the mortality rate is estimated at 2.9%. Treatment of multidrug-resistant TB (MDR-TB) defined as the resistance to the two most effective antiTB drugs, and requires therapy of more than 7 drugs taken on a daily basis during 9–12 months. This study aimed to evaluate the safety profile of treatment regimens used for MDR-TB at Jamot Hospital of Yaounde (JHY). **Methods:** This was a retrospective cohort study of patients treated for MDR-TB at HJY from January 1, 2017, to December 31, 2019. Patients characteristics of the cohort, drugs regimen were collected and described. All possible adverse drug reactions (ADR) were described clinically and by severity grade. **Results:** During the study period, 107 patients were included, and 96 (89.7%) experienced at least one ADR. Most parts of the patients (90) experienced mild or moderate ADR. Hearing loss was the most frequent ADR, and led mostly in aminoglycosides dose reduction (n = 30, 96.7%). Gastrointestinal events were commonly observed during the study period. **Conclusion:** Our findings suggested that ototoxicity was a prominent safety issue during the study period. The implementation of the new short treatment regimen could be effective in reducing the burden of ototoxicity among MDR-TB patients. Nevertheless, new safety issues could emerge.

Keywords: Adverse drug reactions, Cameroon, multidrug-resistant tuberculosis, pharmacovigilance, safety

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Introduction

In the last decades, tuberculosis (TB) which is a lung disease caused by *Mycobacterium tuberculosis* becomes a major public health problem worldwide and especially in Cameroon where its mortality rate is estimated at 2.9%.[1,2] Sneezing, coughing, and spitting are the well-known mode of contamination from person to person.[2] Due to its related morbidity and mortality, this disease has been recognized in 1994 as a global emergency by the World Health Organization (WHO). Ranked among the top ten causes of death worldwide, TB was also identified as the leading cause of death among patients living with acquired immunodeficiency syndrome (AIDS) in 2020.[3,4]

Multidrug-resistant TB (MDR-TB) is a serious and mortal disease characterized by the resistance to the two most effective first-line anti-TB drugs, isoniazid and rifampicin. WHO estimated that 484,000 new cases of MDR-TB were diagnosed in 2020.[2]

Since 2016, WHO recommend a standardized short treatment regimen (STR) of 9–12 months for MDR-TB patients who

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have not been previously treated with second-line drugs and for whom resistance to fluoroquinolones and second-line drugs has not been observed or is considered unlikely.[3]

Despite the narrow monitoring of the observance and the obligation of the directly observed treatment during the entire treatment, MDR-TB therapy remains complex and related to the occurrence of safety issues. Indeed, the high number of drugs taken on daily basis and the length of MDR-TB therapy increase the likelihood of adverse drug reactions (ADRs), mostly ototoxicity and gastrointestinal disorders with symptoms ranging from mild to severe.[4-6]

As there is limited information available on the exact burden of ADR experienced by patients treated for MDR-TB, the first aim of this study was to evaluate the safety profile of treatment regimens used for MDR-TB management in one hospital of Cameroon. Moreover, this study aimed to assess the severity of adverse events related to MDR-TB treatments, and identify adverse events leading to treatment drug discontinuation or regimen modification.

Methods

Study design and data source

This was a retrospective cohort study of patients suffering from MDR-TB who received a treatment regimen at Jamot Hospital of Yaounde (JHY). JHY is the Cameroonian reference hospital for the treatment of TB, and two-thirds (2/3) of MDR-TB cases were treated there. Patients hospitalized between January 1, 2017 and December 31, 2019, were included.

Among them, patients aged with less that 18 years or those with no information available in the medical records were excluded. All information was retrieved from their medical records, which were routinely updated each month.

Patients were followed and data were collected from the 1st day of treatment (Month 1, M1) to: (i) The end of treatment or last visit with available clinical information, (ii) diagnosis of ultra-resistant TB, or (iii) death.

Drug exposure

During the study period the WHO STR was used routinely.[3] This lasts for 9–11 months and is divided into two phases: An intensive in hospital phase, and continuous ambulatory phase. The intensive phase lasted 4–6 months of daily treatment with 6 antibiotics (moxifloxacin, protionamide, isoniazid high-dose, clofazimine, ethambutol, and pyrazinamide) associated with kanamycin or amikacin.

For this study the treatment regimen was categorized in relation to the injectable aminoglycosides or any other drug of choice used during the intensive phase.

The continuous ambulatory phase had a fixed treatment duration of 5 months with 4 antibiotics: Moxifloxacin, clofazimine, ethambutol, and pyrazinamide.

Aside from these guidelines, each drug dose modification or drug switch was described as well as its cause (e.g. ADR or drug shortage).

Safety data

Clinical events that occurred during the study period that patients' practitioners considered as possible ADR and reported in the medical files were collected. ADRs were categorized into digestive, kidney, hepatic, neurological, auditory, and other disorders**.** The physician reported at each visit both ADRs and their severity, using the scale proposed by the French Agency for the Research in AIDS and hepatitis, (National Agency for Research on AIDS and Hepatitis), which corresponds to the first four grades of the Common Terminology Criteria for Adverse Events.[7] As fatal ADRs were not included in this classification, they were considered Grade 5.

Data collection

Data were extracted from medical records in an electronic clinical reporting form, developed using Microsoft office 15.0 Access Database. Three separate sections were produced; the first section was related to the patient's characteristics at baseline namely: sex, age, weight, HIV status, MDR-TB type, TB treatment history, and audiogram status. The second section concerned prescribed treatments, including drug type, doses, eventual switches or dose reduction, start and end date. The third section concerned ADR, with onset month, and severity.

Statistical analysis

A descriptive analysis was conducted on the following variables: gender, mean age and age groups (18–30 years, 31–45 years, 46–60 years, 61–75 years), weight classes (according to the WHO recommendation for drug doses [30–39 kg; 40–54 kg; 55–70 kg; >70 kg]), TB type (Pulmonary [P]; Extra pulmonary [EP]; both or unknown), TB history (patients never treated for TB before, the patient already treated for TB before, or unknown) HIV status, and initial audiogram status (normal, abnormal). The regimen type (e.g. amikacin, or linezolid based) was also described.

All the data were analyzed using R Software, version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/). Participants' baseline characteristics were summarized using frequencies and proportions or mean and standard deviation, depending on the type of the variable. To analyze the differences in patient characteristics by main observed adverse events, we used either chi 2 or Fisher exact test for categorical variables and a 2-sample *t*-test for continuous variables, respectively.

Ethical consideration

The present study was expected to evaluate the safety of drugs used for the treatment of multi-resistant TB. Key information was communicated to the National Program of TB and the Ministry of Public Health, which allowed the beginning of the study.

Results

Study population

During the study period, among 115 potentially eligible patients, five were excluded because no information was available, and three were because they were under 18 year

old. Thus, one hundred and seven patients were included in this study.

Concerning baseline characteristics [Table 1], the sex ratio (M/F) was 1.6 and the mean age was 37 ± 12 years old. Among them, 87 (81.3%) had a pulmonary MDR-TB, one had extrapulmonary and 15 (14.1%) had both MDR-TB. A total of 76 patients (71.0%) had received a TB treatment before becoming MDR-TB. In our cohort, 39 (36.4%) patients were HIV positive, and 45 (42.1%) reported audiogram abnormalities at baseline.

Drug use and switches

A total of 99 patients (92.5%) started the intensive phase with kanamycin base treatment, five patients (4.6%) with linezolid, and three patients (2.8%) with amikacin [Table 2].

Out of the 107 Patients, 30 (28.03%) changed the drug or its doses during the follow-up period, for a total of 34 changes [2 drug switches, 32 changes in drug doses, 31 doses reduction and 1 dose increase, Table 2].

Adverse drug reactions

A total of 96 patients (89.7%) experienced at least one ADR during the study follow-up, mostly of mild or moderate severity grade (n = 90, 84.1%). Two-thirds of the included patients (70 on 107) developed hearing impairment of grade 1 only (38, 35.5%), grade 2 only (14, 13.08%), or both grade 1 and 2 (18, 16.8%). A total of 448 ADRs have been collected from the patient's medical records [4.5 ADR per patient; Table 3].

Hearing impairment was the most frequently related to a drug switch (n = 1, (50%) or a dose reduction (n = 30, 96.7%). Indeed, among drug switches, linezolid was changed with Kanamycin because of drug shortages, while amikacin was changed with kanamycin because hearing impairment.

Among changes in drug doses, the kanamycin dose was reduced 29 times because of hearing impairment; The amikacin dose was reduced because of hearing impairment in one patient, while the pyrazinamid dose was decreased because of hyperuricemia. Moreover, moxifloxacin was contextually increased because of a risk of progression to ultra-drug-resistant TB (dose increase from 400 mg to 800 mg/day).

Six patients (5.6%) experienced ≥ grade 3 adverse events:

Three sudden death

occurred in men with pulmonary TB, aged 19, 28, and 56 years (HIV positive). Two patients died in the 1st month of follow-up, one in the 7th month; two patients weighed 55–70 kg and one 40–54 kg. One patient was treated with a linezolid based-regimen, and others with a kanamycin-based regimen.

Two acute kidney injuries

occurred in men, both aged 33 years, weighed between 55 and 70 kg or >70 kg. One case was associated with HIV-related nephropathy. Both patients were treated with kanamycin-based regimen and both had pulmonary TB. The event occurred for both the 1st month of treatment.

Table 1: Cohort baseline characteristics (n=107)

Characteristics	n (%)
Sex	
Male	67 (62.6)
Female	40 (37.3)
Age	
Age years, mean±SD	37.0±12.0
18–30	39 (36.4)
31–45	43 (40.1)
46–60	21 (19.6)
61–75	4 (3.7)
Weight classes (WHO) (kg)	
30–39	8 (7.5)
40–54	41 (38.5)
55–70	45 (42.05)
>70	13 (12.1)
Type of TB	
Pulmonary	87 (81.3)
Pulmonary and/or extra pulmonary	16 (15.0)
Unknown	4 (3.7)
TB treatment history	
Never treated	26 (24.3)
Already treated	76 (71.0)
Unknown	5 (4.7)
Baseline audiogram status	
Normal	53 (49.5)
Abnormal	45 (42.1)
Unknown	9 (8.4)
HIV status	
Positive	39 (36.4)
Negative	68 (63.6)

WHO: World Health Organization, SD: Standard deviation, TB: Tuberculosis

Table 2: Treatment duration and switch (n=107)

Drug	n (%)
MDR-TB treatment regimen	
Kanamycin based regimen	99 (92.5)
Linezolid based regimen	5 (4.6)
Amikacin based regimen	3 (2.8)
Drug switch or dose change during follow-up	
Yes	26 (24.2)
No	81 (75.7)

MDR-TB: multidrug-resistant tuberculosis

One myocardial infarction

occurred in a man, aged 48, weighted >70 kg, with unknown TB history, and under kanamycin regimen. This event occurred during the 1st month of treatment.

The description of these cases was poor without any element clearly supporting the role of the drugs used for the control of MDR-TB.

Hearing loss

A total of 70 patients (65.4%) developed hearing loss during the study follow-up. Among them, 53 patients (49.5%) were free of any hearing issues at baseline.

Table 3: Adverse drug reaction occurred during multidrug-resistant tuberculosis treatement (*n*=107)

Type of adverse event	Total, *n* (%)	Grade 1, *n* (%)	Grade 2, *n* (%)	Grade 3, *n* (%)	Grade 4, *n* (%)	Grade 5, *n* (%)
Hearing impairment	70 (65.4)	57 (53.2)	32 (30.0)	-	-	-
Vomiting	32 (30.0)	32 (30.0)	-	-	-	-
Nausea	12 (11.2)	12 (11.2)	-	-	-	-
Abdominal pain	6 (5.6)	6 (5.6)	-	-	-	-
Paresthesia	4 (3.7)	4 (3.7)	-	-	-	-
Sudden death NOS	3 (2.8)	-	-	-	-	3 (2.8)
Arthralgia	3 (2.8)	2 (1.8)	1 (0.9)	-	-	-
Duodenal ulcer	3 (2.8)	-	3 (2.8)	-	-	-
Diarrhea	2 (1.8)	2 (1.8)	-	-	-	-
Acute kidney injury	2 (1.8)	-	-	2 (1.9)	-	-
Hyperuricemia	2 (1.8)	2 (1.8)	-	-	-	-
Hepatic enzyme increased	2 (1.8)	2 (1.8)	-	-	-	-
Pruritus	2 (1.8)	2 (1.8)	-	-	-	-
Myocardial infarction	1 (0.9)	-		1 (0.9)	-	-
Sinus tachycardia	1 (0.9)	1 (0.9)	-	-	-	-
Palpitations	1 (0.9)	1 (0.9)	-	-	-	-
Cholestatic icterus	1 (0.9)	1 (0.9)	-	-	-	-
Cataract	1 (0.9)	1 (0.9)	-	-	-	-
Creatinine increased	1 (0.9)	1 (0.9)	-	-	-	-
Dyspepsia	1 (0.9)	-	1 (0.9)	-	-	-
Eye disorders	1 (0.9)	1 (0.9)	-	-	-	-
Glaucoma	1 (0.9)	1 (0.9)	-	-	-	-
Hypersomnia	1 (0.9)	1 (0.9)	-	-	-	-
Hypothyroidism	1 (0.9)	1 (0.9)	-	-	-	-
HIV-associated nephropathy	1 (0.9)	-	-	1 (0.9)	-	-
Knee pain	1 (0.9)	1 (0.9)	-	-	-	-
Vertigo	1 (0.9)	1 (0.9)	-	-	-	-

The most frequent hearing impairment was tinnitus (*n* = 25; 23.3%), followed by hearing loss (*n* = 20; 18.7%), bilateral (11 cases, 10.2%) or mono-lateral (9 cases, 8.4%). For 26 patients (24.2%), the detail of the hearing impairment was not recorded.

Out of the 53 patients who had normal hearing at baseline, 70% (*n* = 37) developed a hearing impairment recorded during the study follow-up. Figure 1 shows the reporting time of hearing impairment according to the study visits. Among patients without any hearing impairment at baseline, 16.9% of patients developed hearing impairment at M1. This rate increase up to 40% at M2, and decreased progressively thereafter. Regarding patient of special interest, out of 28 (71.7%) of the 39 patients living with HIV included in this study faced hearing impairment during their treatment while 42 (61.7%) among the 68 patients without HIV experienced it.

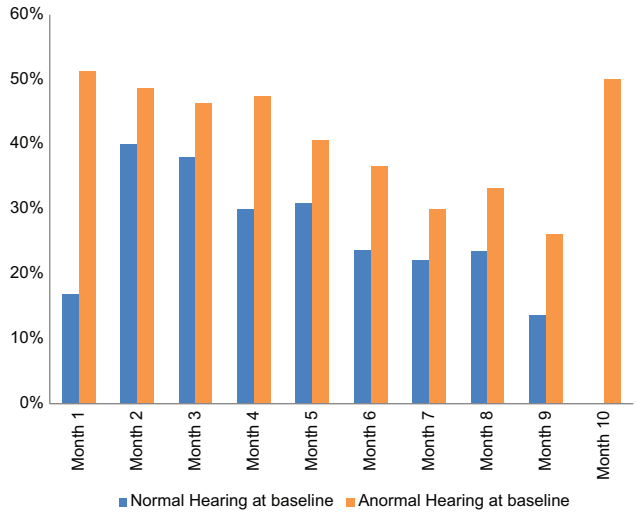

Figure 1: Rates of patients with hearing impairment according to follow-up

Discussion

The key findings showed that most parts of included patients developed an ADR related to the MDR-TB treatments. Most parts of ADR were nonsevere and probably related to aminoglycoside treatment. The dose reduction because of hearing impairment was the most frequent action for individual risk management.

The study cohort seems quite representative of the Cameroonian population affected by MDR-TB. For example, the sex ratio of the patients involved in this study is globally the same as that reported by the Cameroonian statistics in 2019 in which men represent 61% while women represent 39%.[8] Moreover, the mean age was also in line with the national data which ranks

the age of people suffering from TB from 25 to 44 years old. Concerning HIV-TB co-infection, our prevalence is quite higher than the 27% estimated in Cameroon.[8] This could be understood as immunocompromised patients could develop more frequently MDR-TB.[9]

Patients were mainly treated at JHY with the WHO recommended STR with injectable kanamycin as the aminoglycoside of choice during the intensive phase.[10] Among patients that didn't start with kanamycin, three started with amikacin. The latter could be used as an alternative, but is considered at higher risk of ototoxicity.[9,11] Five other patients started with linezolid, which was at the time of the study a well-admitted practice. Indeed in 2018, the international union against TB and lung disease highlighted in their practical guide to the management of resistant TB that delamanid, linezolid, or bedaquiline could be used instead of aminoglycosides.[12] In 2021, Souleymane MB *et al.* showed that, among patients treated in Niger for pulmonary MDR-TB from 2016 to June 2018 with STR, 12.7% had a linezolid-modified STR, both used at the beginning of treatment or after a kanamycin induced hearing loss.[13]

The safety of MDR-TB is thus an issue that has a high impact on prescription practice. The high frequency of ADR observed in this study was quite similar to the study carried out in a tertiary hospital in Italy from 2008 to 2016. In the latter, Gualano G *et al.*, reported that 66 out of 74 patients (89.2%) had experienced ADRs during their treatment.[14] This occurrence rate was nevertheless higher in comparison to others studies. Indeed, in 3 years 2000–2002, a study carried out in Russia reported that 73% of 244 patients experienced ADR from 2006 to 2007, while an Indian study reported an ADR rate of 58%.[15,16]

The present study showed that severe ADRs were infrequent, and accounted for <3%. Almost all severe ADRs occurred during the 1st month of treatment. This finding is not far from the proportion of patients who experienced severe ADRs during the first 6 months reported in Italy.[14] Our study collected also three sudden death, but any objective element was found to relate them to the prescribed drugs.

As reported by several studies, the high frequency of ADR occurrence among MDR-TB patients can lead to drug dose reduction, switch of drugs, or treatment interruption.[14,17] This is particularly observed with hearing loss as it can impact an individual's life by causing social isolation, reduced quality of life, and threatening employment stability and family prosperity.[9] That is corroborated by our findings as we observed that almost all of the observed drug switches and dose reductions were due to hearing impairment and related to kanamycin.

During the study period, ototoxicity was the most frequently reported safety issue, and hearing impairment affected almost two out of three patients. It is well known that a high proportion of MDR-TB patients develop hearing loss due to ototoxicity caused by aminoglycosides used during the STR's intensive phase.[9] However, the rate found in this study is clearly above the 10%–50% of aminoglycosides-induced hearing loss reported in 2018 by WHO from different continents.[18,19]

Several studies have reported that antiretroviral therapy is highly associated with an increased risk of ototoxicity, particularly in sub-Saharan African countries and patients co-infected need narrow and special audiometric monitoring.[9] In our study the prevalence of hearing loss was also slightly increased in patients with HIV compared to the rest of the cohort (71.7% vs. 61.7%).

Regarding the common occurrence of ototoxicity with aminoglycosides, systematic audiometry monitoring is recommended at baseline and during MDR-TB treatment.[18,19] In Cameroon, audiometry was systematically done at baseline, the second, and the 4th month. Nevertheless, even with a high proportion of auditory issues, any case of hearing impairment was reported to the Cameroonian pharmacovigilance system during the study period. Thus, if clinicians in Cameroon are well aware of the importance to carry out audiometric measures, actions are needed to increase the culture of spontaneous reporting that helps authorities to implement adequate risk minimization strategies.

Nowadays, bedaquiline is used in Cameroon as a drug of choice in the intensive phase regimen in alternative to aminoglycoside. In June 2020 WHO recommended a new STR for MDR-TB patients without previous exposure to second-line medicines for more than 1 month, where there is no fluoroquinolone resistance and the patients do not have extensive TB disease or severe extrapulmonary TB.[20] Those WHO recommendations followed the findings of several studies which have shown that the replacement of aminoglycosides with bedaquiline has better efficacy and safety with a high therapeutic success.[21-23] One of the advantages of bedaquiline is the fact it is orally administered allowing for easy administration. Meanwhile this drug reserve also safety issue as adverse events other than hearing impairment have to be monitored, such as QT interval (QTc) prolongation.[23,24] Thus, in Cameroon aminoglycosides were replaced with bedaquiline, and the safety monitoring of this new STR regimen is now mainly based on the control of the cardiac function via standardized ECG at baseline and each month during the treatment period.

This will represent a new challenge for the Cameroonian pharmacovigilance system. Very few cases of ADRs occurred during the study period were reported. In the meantime, these safety data were searched and collected by clinicians. For future safety assessment, new tools could be envisaged in the context of the national TB Control Program, which could allow having data directly in a data warehouse that facilitates data extraction and analysis for data driven regulatory decisions. Besides hearing loss, gastrointestinal events were the most common adverse events observed in this study and affected more or less 1/3 of included patients. These findings are higher than the frequency retrieved in a Vietnamese cross-sectional

study (14.2%).[25] The rate of patients who have developed a nephrotoxic event is also in line with the findings from other studies reporting a prevalence of 4%–10% of nephrotoxicity related to injectable anti-TB drugs.[26-30]

This study has some limitations. The sample size is relatively small, and it was a retrospective study based on already collected data in which some information was lacking, for example, the cause of death, and the evolution of ADRs. Moreover, ADRs were collected during monthly visits; it was thus not possible to correctly identify the actual start of the symptoms and the actual ADR evolution. As the study only aimed to collect ADRs reported by a physician in the medical files, laboratory changes were not systematically sought, thus an underestimation of ADRs needs to be accounted for.

Conclusion

To our knowledge, this study is the first specifically designed to estimate the incidence of ADR among MDR-TB patients in Cameroon, and describe their clinical features. As our findings suggested that ototoxicity was a prominent safety issue, the implementation of the new STR in which aminoglycosides are abandoned could globally reduce the burden of ADRs among MDR-TB patients. Nevertheless, as aminoglycosides were replaced with bedaquiline, new safety issues could emerge. Thus efficient and modern safety data flow need to be implemented in the context of a national program of TB to ensure the patients' safety.

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Ethical clearance

This study obtained approval from the National Tuberculosis Control Program and the Ministry of Public Health.

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Conflicts of interest

There are no conflicts of interest.

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