Adverse Events Associated with Multidrug-Resistant Tuberculosis Treatment in Mali

Événements indésirables associés au traitement de la tuberculose multirésistante au Mali

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Résumé :
L'objectif de cette étude a été de déterminer l'incidence des effets indésirables et leur impact sur le traitement de la tuberculose multirésistante (TB-MR) au service de pneumo-phtisiologie du CHU du Point-G. Une étude transversale prospective a été menée de janvier 2018 à août 2019 et les participants à l'étude étaient tous, des patients hospitalisés et ayant reçu un traitement standardisé de 9 mois. Les événements indésirables ont été évalués sur la base de critères cliniques et paracliniques et l'évaluation de la causalité des effets indésirables médicamenteux (EIM) a été réalisée à l'aide de l'algorithme de l'Organisation mondiale de la santé. Les événements indésirables ont été enregistrés chez 86,2 % (n=31) des patients, dont l'âge moyen était de 40 ans (de 18 à 77 ans). Les effets indésirables observés étaient les troubles digestifs (37,3 %), suivis de la douleur lors de l'injection (19,3 %). Une toxicité de grade IV de l'OMS, à savoir une perte auditive (surdité mixte ou bilatérale) a été observée chez 3,62% (n=3) des cas. La causalité des effets indésirables de l'OMS était "probable et possible" dans 24,1 % (n=20). La prise en charge de ces EIM a consisté en des conseils et la prescription d'antihistaminiques. L'évolution a été favorable dans 42 % des cas, mais la létalité a été de 5,6 %. Un système national de pharmacovigilance est nécessaire pour améliorer la gestion des EIM graves dans ce groupe de patients.
Mots-clés : Effets indésirables, tuberculose multirésistante, médicaments antituberculeux de deuxième intention, Mali.

Abstract:
This study aimed to determine the incidence of adverse effects and their impact on the treatment of multidrug resistant tuberculosis (MDR-TB) in the department of pneumology at the teaching Hospital of Point-G. A prospective cross-sectional study was conducted from January 2018 to August 2019 and the participants were all hospitalized MDR-TB patients and receiving a 9-months standardized shorter MDR-TB regimen. Adverse Drug Reaction (ADR) were assessed based on clinical and laboratory outcomes and the assessment of ADR causality was performed using the World Health Organization algorithm. Adverse events were recorded in 86.2% (n=31) of patients, with an average age of 40 years old (ranging from 18 to 77 years). The most observed adverse events were digestive disorders with 37.3%, followed by pain upon injection (19.3%). WHO grade IV toxicity of hearing loss (mixed or bilateral deafness) was observed in 3.62% (n=3) of participants. The causality of the WHO adverse events was "probable and possible" in 24.1% (n=20). Management of these adverse events consisted of counseling and antihistamine drugs prescription. The evolution was favorable in 42% of cases, however the fatality rate was 5.6%. Various adverse events were observed in this study population. Therefore, special attention through pharmacovigilance is needed to improve the management of serious adverse events in this group of patients.
Keywords: Adverse events, MDR-TB, TB Treatment, second-line anti-tuberculosis drugs, Mali.

1. Introduction

According to World Health Organization (WHO), tuberculosis (TB) is a chronic inflammatory disease caused by the infection of the complex *Mycobacterium tuberculosis* [1]. It is a contagious disease transmitted through the respiratory tract [2]. Tuberculosis is one of the leading cause of death from a single infectious agent worldwide, with approximately 1.23 million deaths in 2024 [1]. The treatment of TB is based on a combination therapy comprising several anti-tuberculosis drugs for at least six months of therapy

[3]. Despite its effectiveness, antituberculosis therapy faces several obstacles, such as treatment adherence, therapy duration, adverse events, and the management of dormant bacillus [4]. The commonly enounced reason for the occurrence of resistance is the non-adherence with the treatment regimens [1]. These barriers (such as treatment adherence, therapy duration, adverse events, and the management of dormant bacillus) lead to the treatment failure, enhancing drug-resistant germs emergence. Resistance to antibiotics is the ability of a pathogen to survive the effects of antibiotics. In the case of tuberculosis, resistance originates from spontaneous gene mutations in *Mycobacterium tuberculosis* (MTB) genome, which make the bacteria resistant to the most used antituberculosis drugs. The contagiousness decreases rapidly after starting the treatment; however, isolation measures may be essential in some cases. Multi-Drug Resistance Tuberculosis (MDR-TB) is defined as simultaneous resistance to at least Rifampicin and Isoniazid [1]. WHO estimates, at 3.5%, the incidence of MDR-TB for new TB cases and 20.5% for previously treated cases [1]. For the most affected countries, the priority is still given to curative care for MDR-TB and Extensively Drug Resistance TB (XDR-TB) [5]. In Mali, the MDR-TB prevalence was 3.4 % and 66.3% for new and previously treated patients respectively [6]. Since January 2018, Mali adopted a short (9 months) MDR-TB treatment regimen. The treatment regimen consists of two phases: A first phase of 4 months, combining Kanamycin (Km), Moxifloxacin 400 mg (Mfx), Prothionamide 250 mg (Pto), high-dose Isoniazid (H) 300 mg, Clofazimine 100mg (Cfz), Ethambutol 400mg (E) and Pyrazinamide 400 mg (Z). A second phase of 5 months of Mfx: 400 mg, Cfz: 100 mg, E: 400 mg and Z: 400 mg.

The second-line TB drugs are molecules belonging to various chemical classes, active on *Mycobacterium sp,* used after a failure of first-line drugs. They are considered to be more effective and/or more toxic [5]. Herein, we attempted to assess the adverse events due to second-line anti-tuberculosis drugs in patients with MDR-TB at one of the teaching Hospitals of Bamako, Mali. In this study, we determined the incidence of adverse events and their impact on multidrug-resistant tuberculosis (MDR-TB) treatment at the department of Pneumo-phtisiology of the Teaching Hospital of Point-G, Bamako.

2. Methods

A cross-sectional study was conducted between January 2018 and August 2019 at the MDR-TB unit of the department of Pneumo-phtisiology, Bamako, Mali. The Unit, with 33 beds, receives and treats all MDR-TB patients diagnosed across the country (Mali).

Patients diagnosed with MDR-TB who initiated their 9-month treatment regimen less than one month, who were hospitalized at the MDR-TB Unit during the study period, that consented to participate were included in this study.

Socio-demographics, clinical and adverse events data were collected. An adverse event was defined as a patient's harmful and undesirable reaction or response after taking a recommended dose of MDR-TB medication for therapeutic purposes. Causality was assessed using WHO criteria which is classified in six degrees as follows: (I) certain, (II) probable, (III) possible, (IV) improbable, (V) conditional and (VI) non-evaluable. A causality chart was used to confirm an adverse event and a questionary was used to collect qualitative and quantitative data, which were cleaned using Excel, coded, and analyzed using SPSS 16.0.

The study was approved by the ethics committee of the Faculty of Medicine and Odonto-Stomatology (FMOS) and the Faculty of Pharmacy (FMOS/FAPH) of the University of Science, Techniques and Technologies of Bamako (USTTB), Mali.

The study protocol was reviewed and approved by the Ethics Committee of the Faculty of Medicine, Pharmacy and Dentistry of the USTTB (N° 59CE/FMPOS).

Patients were only included in the study after providing signed consent forms according to the Helsinki declaration.

3. Results

3.1. Participants socio-demographic characteristics

A total of 36 participants were included during the study period. The social and demographic characteristics of the participants are represented in table I. Males were more presented than than women (83%) with an average age of 40±13 years old. More than half of the study participants (55.56%) came from diverse regions of Mali, and the remaining were from the capital city of Mali (Bamako). HIV coinfection was observed in 22.23% patients. The average weight of the patients during this study was 54 kg.

Table I: Sociodemographic characteristics of patients

Characteristics		Number	Percentage
Sex	Male	30	83.34
	Female	6	16.66
Age range	< 20 years	2	5.55
	21-40 years	20	55.56
	41-60 years	12	33.34
	61-80 years	2	5.55
Weight	< 40 kg	3	8.33
	41-60 kg	26	72.23
	>60 kg	7	19.44
Residence	Bamako	16	44.44
	Outside Bamako	20	55.56
Comorbidities	VIH	8	22.23
	Diabetes	2	5.55
Adverse events	Yes	31	86.2
	No	5	13.8

3.2. Recorded adverse events during the MDR-TB treatment

Adverse events were observed in 31/36 (86.2%) participants, with a total of 83 events observed led by digestive disorders (33.7%). The antituberculosis drugs involved in the adverse events are presented in table II, according to the WHO grades.

Based on the WHO causalities criteria of adverse events, these 83 events were distributed into the six degrees (table III). Probable and possible cases were the most observed with both 24.1%, and Certain was observed 21.7%. One of the events was nonevaluable (1.2%).

Table II: Distribution of adverse events according to WHO grade of toxicity and incriminated molecules.

Adverse events		Grade I	Grade II	Grade III	Grade IV	Incriminated molecules
Clinic	Clinic	n=39	n=22	n=19	n=3	-
Digestive	Nausea	7	0	2	0	Pto, Z, Cfz, Km
	Vomiting	6	5	3	0	-
	Epigastralgia	2	0	3	0	Pto, H, E, Z
Skin	Pain	8	3	4	1	Km, Z, H, Pto
Respiratory	Dyspnea	3	7	2	0	Mfx
Ototoxicity	Buzzing	2	6	2	2	Km, H
Mental disorder	Dizziness	2	0	1	0	H, Pto
	Insomnia	3	0	1	0	H, Pto
	Anorexia	6	1	1	0	Pto, Mfx

Km *(Kanamycin);* ***Mfx*** *(Moxifloxacin);* ***Pto*** *(Prothionamide);* ***H*** *(high-dose Isoniazid);* ***Cfz*** *(Clofazimine);* ***E*** *(Ethambutol);* ***Z*** *(Pyrazinamide).*

Table III: Causality of adverse events according to WHO criteria

Imputation	Number (N=83)	Percentage (%)
Certain	18	21.7
Probable	20	24.1
Possible	20	24.1
Improbable	10	12
Conditional	14	16.9
Non-evaluable	1	1.2

3.3. Evolutionary trend of the adverse events and outcome of MDR-TB treatment of patients.

The evolution of the adverse events was favorable in 42% of the cases, followed by regression, stationary and sequela, as shown in figure 1. The outcome was unknown in 14% of patients under the MRD-TB treatment regimen.

MDR-TB treatment was successful in 14 patients and 18 patients were in favorable health condition. We noted 2 deaths and 2 patients recovered with sequela (see figure 2).

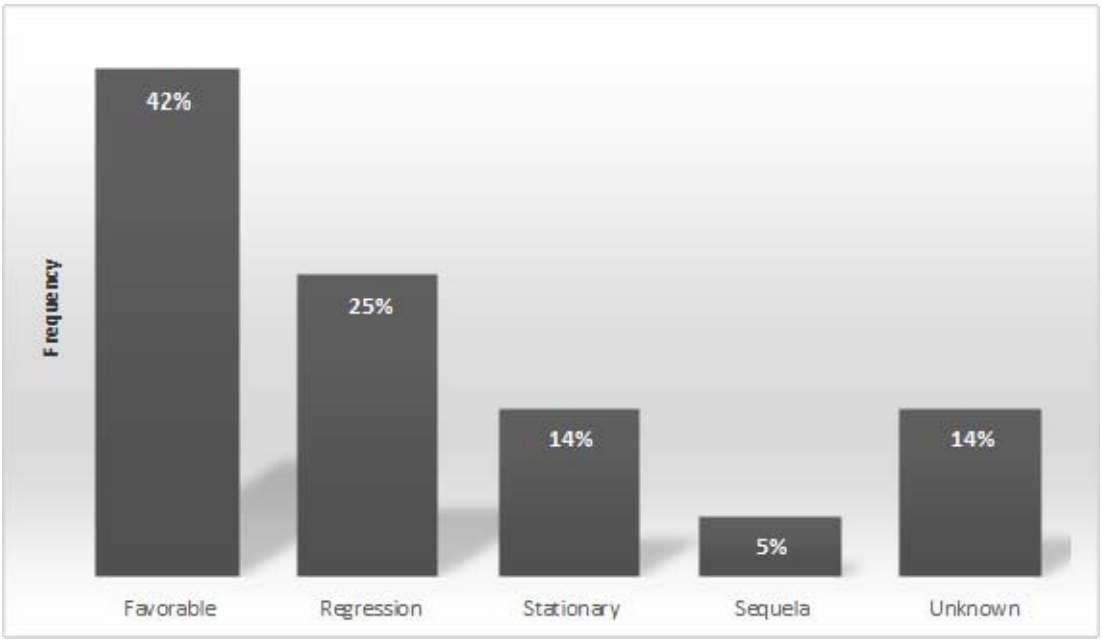

Figure 1: *Outcome of adverse events observed in patients*

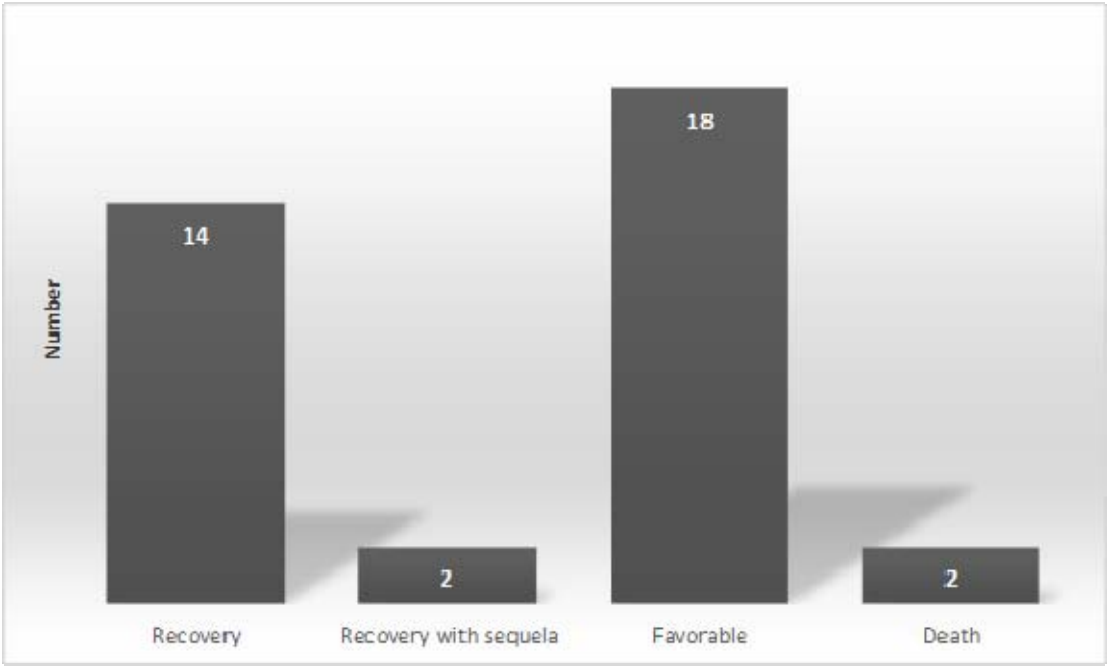

Figure 2*: Clinical status of patients after MDR-TB treatment*

4. Discussion

36 patients were included in this study and male were more prevalent. As stated by various studies, tuberculosis disease (TB), is more common among males than females [6, 7]. The most represented age group was ranked from 21 to 40 representing 55.6% of the study participants. Elsewhere, Ruddy *et al.*, [8] reported 60%, and Ouédraogo *et al.*,[9] mentioned 80.4% of people that were under 50 years. This implies that the population under 50 years old is really concerned by this scourge of TB and most particularly by

MDR-TB. The average weight of the patients was 54 kg; Sagwa *et al*., [10] also reported participants' weight to be (52,5 ± 11,3 Kg) in one of their studies.

Tuberculosis and HIV coinfection cases were notified in our study population, with 22.2% of the patients coinfected, which was higher than the 16.06% reported by Gandhi *et al.*,[11] in patients with pharmaco-resistant TB. Nevertheless, the result of HIV/TB coinfection observed in our study participants with MDR-TB is less than which described in Southern Africa and in South-East Asia, where HIV has a high prevalence [12-15]. This variation is due to the specificity of the study's young population and the high prevalence of HIV in these regions. Moreover, we found that 5.6% of the MDR-TB patients were associated with diabetes.

The mean aim of this study was to examine the association of adverse events with the second line MDR-TB drugs. Diverse adverse events were recorded in 31 patients (86.2%). The most frequent adverse event was pain at the injection site, followed by vomiting. More than 36.1% had an onset time of less than one week, followed by onset on taking the drug in 13.9%. These events were mild in most cases. We recorded 3 cases of grade IV events that led to discontinuation of the drug and adequate treatment of the patient. The use of new oral anti-tuberculosis drugs could reduce the rate of injection site pain. This result is similar to the 86% and 80.3% reported respectively by Nathanson [16] and Ouédraogo *et al.,*[9]. Several studies stated a variety in the prevalence of adverse events between 63% and 96% [17-21]. The reason for this heterogeneity in the prevalence of adverse events is unclear but could be due to the definition of adverse events as any abnormality symptomatic or not, reported or not, and severe or not.

The patients who presented digestive events were the most frequent, including vomiting, followed by nausea and epigastralgia. We did not observe any cases of abdominal pain in our study associated with the second-line regimen. The mode and route of use (injectable) of the second-line drugs could explain this. Among the recorded events, digestive disorders represented 33.7.% similar to Ouédraogo et *al*, Piubello *et al*., and Shin et *al*, findings, respectively 35.2%, 26.2%, and 47.3% [9, 22, 23]. The average time of onset of the event was 2 days. The number of tablets (10-15 per patient) to be taken once on an empty stomach for the MDR-TB patient may play a role in the onset of these digestive problems in order of increase.

Pain upon injection represented 19.3% of adverse events, higher than the 6.2% found by Piubello *et al.,*,[22] and 13.4% by Bloss *et al.*,[17]. Conversely, our result is less than the 47.9% recorded by Ouédraogo *et al*.,[9]. These differences could be explained by the site of pain recorded in our study population: ocular, abdominal, lumbar, articular, and injection sites. Some of these pains were classified as grade IV toxicity based on WHO criteria.

Ear buzzing represented 14.5% of all adverse events. This result was comparable to the 15.5%, and 15.6% found respectively by Ouédraogo *et al*.,[9], and Shin et *al*,[23]. Other studies reported varying results 5.1%, 17.8%, 20%, 24%, and 41.6%[16, 22, 24-26]. The high prevalence of tinnitus found in these studies is certainly due to patient self-reporting of the symptom, which is subjective, and audiometric tests may not have validated them. In addition, the event may be due to interaction with other concomitant and potentially ototoxic drugs used in tuberculosis regimens, such as fluoroquinolones[10].

We found exertional dyspnea in 14.5%. This result is close to 16.1% found by Yoon et *al*,[27]. All molecules included in the second-line anti-tuberculosis regimen are presumed to be responsible for digestive disorders[10, 22]. Pyrazinamide (Z) and/or Kanamycin (Km) are presumed to be responsible for pain[18, 22]. Isoniazid (INH) and/or Prothionamide (Pto) for mental disorders[18]. Kanamycin (Km) and/or Isoniazid (INH) for ringing in the ears[28]. Moxifloxacin (Mfx) is presumed to be responsible for exertional dyspnea[27].

Based on WHO criteria, 18 adverse reactions were likely and possibly related to drugs which represent 24.1% in our study. This frequency does not reflect reality because there are factors favoring undesirable effects such as co-morbidity and the accuracy of the determination of the levels of accountability according to the WHO guideline.

Grade I, II, and III adverse events were more observed in our population, and many other studies reported similar results [29,30]. We counted three grade IV adverse events (3.62%). They were 2 ears buzzing and 1 auricular pain. Several studies also reported other severe toxicity due to MDR-TB treatment [20, 22, 29, 30].

The management of adverse events in our patients was curative or symptomatic depending on their grade of toxicity recorded during the daily follow up. Grade III adverse events required medical prescription such as antihistamines, antiemetic, NSAIDs. Symptomatically or curatively management of adverse events were also reported in several studies [18, 23, 31]. In other studies, drugs incriminated to cause grade IV toxicity were either stopped, substituted, dose reduced, or frequency reduced[19, 26, 32]. The outcome of adverse events was favorable in 42% of cases in our population, similar to findings in other studies [9, 17, 21]. Symptom regression was 25% and 5% for sequela. Sequela was auricular (mix, sometimes bilateral deafness). Piubello *et al.*[22], reported a hearing loss in 15.5%. Cochleovestibular involvement in 43.2% of cases was reported by Ouédraogo et al[9]. Toloba *et al*.,[31] found a deafness case in Mali. Rakotomizao *et al*,[26] reported hearing impairment with severity varying from buzzing in the ears, dizziness to deafness (41.6%).

The clinical status of patients was favorable in 50% of cases. The recovery rate was 44.4% including 5.6% with sequela. Several studies have also recorded a favorable clinical condition of patients [22, 23, 33]. The lethality rate was 5.6% in our series, similar to 5.5% of Benmoussa et *al,* [33] and is close to 6.4% obtained by Berdous et *al*,[34]. Kakou *et al*., found a higher lethality rate of 37.3% [35] in MDR patients with HIV co-infection suggesting that HIV coinfection increase the mortality rate.

Study limit: Therapeutic choice to treat MDR-TB are limited. Some active antibiotics are less efficient than Isoniazid and Rifampicin and found to be more toxicity. This may lead to many adverse events responsible for treatment failure as they can be subject to non-adherence of patients to treatment. The small size of the sample and the lack of means for measuring the concentrations of antituberculosis drugs were limitations of this study. The sample size and the absence of blood concentration measurements do not prevent the description of ADRs and the expression of conclusive results in our context. Another limitation was the WHO causality method used.

5. Conclusion

This study found a higher rate of ADR in MDR-TB management in Mali, which confirm that the second line anti-TB regimens are subject to Severe ADR. Nevertheless, WHO grade IV toxicity events were observed, suggesting the need of national pharmacovigilance system.

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