

Adverse drug reactions and patients' outcomes in Moroccan tuberculosis cases

Effets indésirables des médicaments antituberculeux et évolution des patients avec tuberculose au Maroc

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ABSTRACT

Introduction: Tuberculosis (TB) remains a global health problem. Its treatment usually involves a combination of antibiotics over a prolonged period, exposing patients to a range of adverse drug reactions (ADRs).

Aim: To investigate the epidemiology and outcomes of tuberculosis patients in Rabat (Morocco), with particular emphasis on assessing the ADRs of treatment and factors contributing to their occurrence.

Methods: This retrospective study was conducted at Moulay Youssef Hospital in Rabat, from January 2021 to May 2022. Only patients hospitalized in the intensive phase of tuberculosis treatment, with known HIV status, and aged 15 or over were included. Sociodemographic characteristics, clinical presentations, manifestations of ADRs, and patient outcomes were analyzed. Uni- and multivariate logistic regression were conducted to identify factors associated with ADR occurrence.

Results: In this study, 144 patients were included. The mean age of patients was 45.82±19.26 years. A male predominance was observed with a sex ratio of 1.4. Almost one-third of the patients (31.5%) experienced at least one ADR during treatment, with gastrointestinal symptoms (50%) being prominent. Logistic regression identified higher ADR incidence in females (p-value=0.046, OR=2.123; 95%CI: 1.013-4.448) and patients with addictive habits (p-value=0.019, OR=3.358; 95%CI:1.478-8.419). Treatment success was observed in 64.58% of the cases, with ADRs showing no significant difference between patients with successful treatment and those with failed treatment.

Conclusion: The occurrence of ADR poses a significant challenge to tuberculosis patients, highlighting the need for personalized approaches to mitigate these complications and ensure treatment success.

Key words: Tuberculosis; Epidemiology; Adverse drug reactions; Morocco

RÉSUMÉ

Introduction: La tuberculose (TB) demeure un défi majeur de santé publique dans le monde. Son traitement implique généralement une combinaison d'antibiotiques sur une période prolongée, exposant les patients à une série d'effets indésirables des médicaments (EIM).

Objectif: Cette étude vise à étudier l'épidémiologie et l'évolution des patients atteints de tuberculose à Rabat (Maroc), en mettant particulièrement l'accent sur l'évaluation des effets indésirables du traitement et les facteurs contribuant à leur apparition.

Méthodes: Cette étude rétrospective a été menée à l'hôpital Moulay Youssef de Rabat, de Janvier 2021 à Mai 2022. Seuls les patients hospitalisés en phase intensive de traitement de la tuberculose, ayant un statut VIH connu et âgés de 15 ans ou plus ont été inclus. Les caractéristiques sociodémographiques, les présentations cliniques, les manifestations des EIM et les résultats du traitement ont été analysés. Des régressions logistiques uni- et multivariées ont été réalisées pour identifier les facteurs associés à l'apparition des EIM.

Résultats: Dans cette étude, 144 patients ont été inclus. L'âge moyen des patients était de 45,82±19,26 ans. Une prédominance masculine a été observée avec un sex-ratio de 1,4. Près d'un tiers des patients (31,5%) ont présenté au moins un effet indésirable pendant le traitement, les symptômes gastro-intestinaux (50%) étant les plus fréquents. La régression logistique a identifié une incidence plus élevée d'EIM chez les femmes (p=0,046, OR=2,123 ; 95%CI : 1,013-4,448) et les patients ayant des habitudes toxiques (p=0,019, OR=3,358 ; 95%CI:1,478-8,419). Le succès du traitement a été observé dans 64,58 % des cas.

Conclusions: L'apparition d'effets indésirables constitue un défi important pour les patients atteints de la tuberculose, soulignant la nécessité d'approches personnalisées pour atténuer ces complications et garantir le succès du traitement.

Mots clés: Tuberculose ; Épidémiologie ; Effets indésirables des médicaments ; Maroc

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INTRODUCTION

Tuberculosis (TB) is an ancient and highly infectious disease caused by *Mycobacterium tuberculosis* (1). It persists as a global health problem affecting millions worldwide (2). According to the World Health Organization (WHO), TB ranks among the top ten causes of death worldwide (3). As of 2022, approximately 10.6 million new TB cases were reported globally, with 1.3 million deaths attributed to this disease (3). In addition to its impact on individual health, this infection involves societal and economic dimensions.

In Morocco, Tuberculosis, mainly the pulmonary form, remains one of the most preoccupying infectious diseases, with high incidence and mortality rates. This infection represents a real challenge for the country's healthcare system, notably due to the presence of several risk factors in our context, including poverty, population density in certain regions, and HIV infection. In 2021, 35,000 cases were registered nationwide, with an incidence rate of 94 per 100,000, ranking Morocco among countries with an intermediate incidence of tuberculosis (4).

There are two distinct clinical forms of tuberculosis: pulmonary tuberculosis (PTB), which affects the lungs and is highly contagious, and extrapulmonary tuberculosis (EPTB), which occurs outside the lungs and has symptoms depending on the affected site. EPTB presents diagnostic challenges due to its varied and non-specific symptoms (1). Both forms of TB require prompt diagnosis and appropriate treatment to prevent complications and transmission of the disease.

Despite considerable progress in the control of this infection, tuberculosis continues to have a disproportionate impact on vulnerable populations, particularly in low- and middle-income countries. Socioeconomic determinants, such as poverty, limited access to healthcare services, and individual immune status, form a set of risk factors that increase vulnerability to infection (2).

Tuberculosis treatment requires a combination of antibiotics administered over a long period. While these drugs are indispensable for curing the infection, they can also cause many adverse drug reactions (ADRs) (5). An ADR refers to "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product" (6). Risk factors associated with ADRs of tuberculosis treatment include age, nutritional status, pre-existing comorbidities, HIV co-infection, EPTB, and retreated TB (5,7,8). Specific ADRs may vary according to the drugs used and the individual's response to treatment, and range from minor symptoms including gastrointestinal disorders or skin rashes to serious reactions such as hepatotoxicity (9). As a result, the occurrence of ADRs can lead to treatment interruption contributing to treatment failure, the development of resistant strains, and increased morbidity and mortality (5). Aware of the seriousness of these ADRs, the Moroccan Ministry of Health has

implemented several measures to better manage them. These measures include the training of nursing staff involved in the administration of anti-tuberculosis treatments, closely monitoring patients under treatment, notifying all detected cases, and ensuring the availability of drugs used to manage these effects (4).

Several studies worldwide and in Morocco have evaluated the ADRs of anti-tuberculosis drugs, but those assessing the factors favoring the appearance of ADRs in our country are scarce (10). Such investigations will help better understand these effects in our context to improve management and patient outcomes. This study aims to investigate the epidemiology and clinical outcomes of tuberculosis patients in Rabat (Morocco), with particular emphasis on describing the ADRs of treatment and factors contributing to their occurrence.

METHODS

Study site and setting

This study was a retrospective review of TB cases notified at Moulay Youssef Hospital from January 2021 to May 2022. The Moulay Youssef Hospital is a tertiary care center located in the Rabat Sale Kenitra region, the second-largest region in Morocco by population and tuberculosis notifications cases in 2021 (4). Only patients over the age of 15 are admitted to the hospital.

Patient inclusion

We included all patients (aged over 15 years) diagnosed with TB and hospitalized in the intensive phase of tuberculosis treatment (n=167). Among them, 144 patients were retained for analysis and 23 were excluded because of incomplete drug records or unmentioned HIV status in the file.

Data collection

Data was obtained from the patient's medical records. The data collected were as follows: i) Sociodemographic characteristics: age, sex, marital status, profession, socioeconomic level, and health insurance; ii) addictive habits: smoking status, alcohol, and cannabis consumption; iii) clinical symptomatology, which included all symptoms present in the patient and linked to the disease, such as cough, dyspnea, chest pain, hemoptysis, and weight loss; iv) comorbidities: HIV-status, diabetes, arterial hypertension, pulmonary disease (asthma, chronic obstructive pulmonary disease, lung cancer, pneumonia), and psychological disorder; v) presentation of the disease: previous history of tuberculosis and the form of the disease (PTB or EPTB); vi) adverse drug reactions (ADRs) of the treatment including any harmful response to the treatment used, such as liver toxicity, peripheral neuropathy, allergic reactions, and gastrointestinal symptoms; vii) patients' outcomes.

TB diagnosis and treatment

Diagnosis of tuberculosis in Morocco is based on bacilloscopy, Xpert-MTB/RIF, and solid culture⁴. The standardized treatment protocol for TB in Morocco follows WHO recommendations which involve two phases of treatment (11):

First line phase: Two- to three-month intensive phase with isoniazid (INH), rifampicin, ethambutol, and pyrazinamide.

Additional first-line phase: Four- to ten-month continuation phase with INH and rifampicin. During the treatment period, ADRs were monitored daily. When symptoms of ADRs are suspected, the treatment is either discontinued or symptomatic treatment is prescribed.

Treatment outcomes were defined and classified based on WHO guidelines (12).

- A cured patient: PTB patient whose tuberculosis was bacteriologically confirmed at the start of treatment and whose smear or culture was negative during the last month of treatment and at least once previously.
- Treatment completed: A TB patient who has completed treatment with no evidence of failure but without negative sputum smear or culture results during the last month of treatment and at least once before.
- Treatment failed: A tuberculosis patient with a positive sputum smear or culture at five months or later during treatment.
- Died: A patient with tuberculosis who dies for any reason before or during treatment.
- Lost to follow-up: A tuberculosis patient who has not started treatment or whose treatment has been interrupted for two consecutive months or more.
- Treatment success: the sum of cured and treatment completed.
- Treatment failure: the sum of treatment failed, died, and lost to follow-up.

Statistical analysis

Quantitative variables were represented by means and standard deviations ($m \pm SD$), and qualitative variables by frequencies (n) and percentages (%). To identify differences between patients with PTB and those with EPTB, we compared categorical variables using the chi-square or Fisher test. To compare the variable age between the two groups, a student's t-test was used since the distribution was normal.

To assess the factors influencing ADR occurrence in our series, we first analyzed the main predictors of ADRs by univariate analysis. All independent variables with a p -value < 0.15 in the univariate analysis were introduced in the multivariate analysis. However, we forced HIV status and the presence of comorbidities into the multivariate analysis model.

To compare the variable ADR occurrence between the group with successful treatment and the group with failed treatment, the chi-square test was used.

A p -value of less than 0.05 was considered significant. All data were analyzed using SPSS.

Ethics consideration

We obtained the necessary authorizations from the Moroccan Ministry of Health to access patient files. Data processing was carried out with respect for patient confidentiality and anonymity, in accordance with the principles of the Helsinki Declaration (13).

RESULTS

During the study period, 144 patients were enrolled, of which 118 (81.9%) were newly diagnosed, and 26 (18.1%) had been previously treated. The mean age of patients was 45.82 ± 19.26 years, with age extreme ranging from 15 to 90 years. Nearly a third of cases (31.25%) were 25 to 34 years old. A higher male incidence was observed with a sex ratio of 1.4. Sociodemographic data revealed that 60.60% of cases were married, with the majority (80.30%) belonging to low-income categories. At the time of management of the TB patients, 61.70% were covered by the health insurance scheme for the economically deprived, and 22.70% had no health insurance. Table 1 presents the clinical and sociodemographic characteristics of TB patients.

Chest radiology revealed abnormalities in 95.72% of PTB cases. This form of TB was the most frequent in our series, with 67.4% of cases. Of the 47 (32.60%) patients with EPTB, pleura was the most frequent site of infection (38.30%). The HIV status of all patients was known, with eight patients co-infected with HIV, corresponding to 5.6% of the study population. In addition, one patient suffered from hepatitis B and another from hepatitis C. For other comorbidities, 40.28% of patients had at least one comorbidity, with diabetes noted in 11.80%.

In terms of addictive habits, active smoking was reported in 52 patients (37.71%) and passive smoking in 2 (1.42%). A combination of tobacco with cannabis and tobacco with alcohol was noted in 11 (7.85%) and 3 (2.14%) patients, respectively. When comparing patients according to the form of TB (pulmonary vs extrapulmonary), cases with PTB were more likely to be previously treated for tuberculosis ($p=0.021$) and have addictive habits ($p=0.05$). EPTB patients were more infected by HIV ($p=0.009$).

Of the 144 TB patients, almost a third (31.5%) reported at least one adverse drug reaction (ADR) associated with anti-tuberculosis treatment. The most frequent ADRs reported were gastrointestinal symptoms (50%), liver toxicity (15%), and skin manifestations (20%). The ADRs of the study population are detailed in Figure 1. Patients who experienced ADRs were 40 years old or younger, 55% were women, and 25% had addictive habits. The sociodemographic and clinical characteristics of patients with and without ADRs are detailed in Table 2.

According to the logistic regression results (Table 2), the incidence of these reactions was two times higher in females (p -value=0.046, OR=2.214; 95%CI: 1.041-4.635) and three times higher in patients with addictive habits (p -value=0.019, OR=3.358; 95%CI: 1.478-8.419). Neither HIV co-infection nor the presence of comorbidities affected the occurrence of ADRs in our series.

Table 1. Socio-demographic and clinical characteristics of the study population

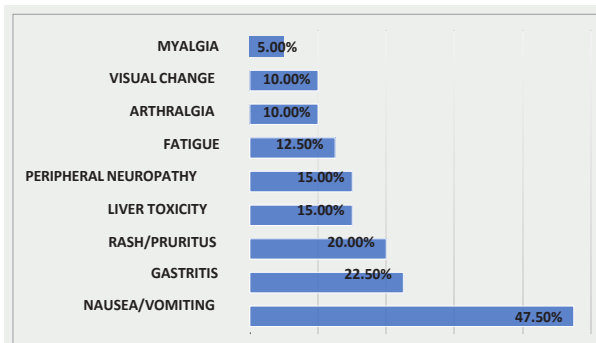
Characteristics	N (%)
Age (m* ± SD**)	45.82 ± 19.26
Age group	
≤ 40	68 (47.22)
>40	76 (52.78)
Sex	
Female	60 (41.70)
Male	84 (58.30)
Residence	
Urban	133 (92.36)
Rural	11 (07.64)
Employment	
Employed	62 (43.06)
Unemployed	82 (56.94)
Clinical symptomatology	
Cough	39 (27.08)
Dyspnea	35 (24.31)
Weight loss	23 (15.97)
Chest pain	11 (7.64)
Hemoptysis	10 (6.94)
HIV*** status	
Positive	08 (5.56)
Negative	136 (94.44)
Comorbidities	
Diabetes	17 (11.80)
Arterial hypertension	11(7.64)
Another pulmonary disease	08 (5.55)
Psychological disorder	04 (2.78)
Other	13 (9.03)
Site of the disease	
Pulmonary	97 (67.36)
Extrapulmonary	47 (32.64)
Pleuritis	18 (38.30)
Lymphadenitis	04 (08.51)
Meningitis	02 (04.25)
Peritonitis	02 (04.25)
Pericarditis	02 (04.25)
Ocular	02 (04.25)
Genitourinary	02 (04.25)
Other sites	15 (31.91)

*Mean

**Standard deviation

***Human Immunodeficiency Virus

Patient outcomes showed that treatment was successful in 93 (64.58%) patients, with 21 (22.58%) cured and 72 (77.42%) completing treatment. More than a third of patients (n=51; 35.42%) had poor outcomes, with 18 (35.29%) dying before the end of treatment, 30 (58.82%) patients experiencing treatment failure, and 3 (2.08%) patients lost to follow-up. There was no significant difference ($p=0.205$) between patients with failed treatment and those with successful treatment in terms of the occurrence of ADRs.

**Figure 1.** Distribution of side effects in the study population

DISCUSSION

In this study, we investigated the epidemiological profile of tuberculosis in Morocco, focusing on the occurrence of ADRs associated with anti-tuberculosis treatment and patients' outcomes in a tertiary care hospital. Tuberculosis continues to pose a serious public health problem in Morocco, with high morbidity and mortality rates (4). The emergence of treatment-resistant strains and the ADRs of anti-tuberculosis drugs further complicate the management and follow-up of patients, making the situation even more complex to control (4).

The study of demographic and clinical characteristics in our series showed that men were more affected by tuberculosis than women. This male predominance has been frequently mentioned in other studies with a sex ratio as high as 2.52 (14). A meta-analysis study assessing the gender difference in tuberculosis burden in low- and middle-income countries concluded that it is necessary to consider this excess of tuberculosis in men and improve their access to health services to reduce the incidence and mortality of this disease (15). PTB was more frequent in our cases, which is in line with international and African literature reporting 87% in Cameroun and 86% in Senegal (16,17). This prevalence of pulmonary localization is due to the specific affinity of *Mycobacterium tuberculosis* for pulmonary parenchyma, and the underdiagnosis of extrapulmonary forms, often requiring invasive techniques (18).

Consistent with previous findings, EPTB was significantly frequent in patients infected with HIV in our study (19). While cases with PTB were more likely to be previously treated for tuberculosis and had addictive habits. The recurrence of PTB in patients already treated was demonstrated in other studies which found that these patients suffer more from treatment failure and the emergence of resistant strains (20). Also, it has been reported in several studies that PTB is associated with addictive habits, including smoking, alcohol, and other drugs (21).

Of the 144 patients enrolled in our research, adverse drug reactions (ADRs) associated with anti-TB treatment occurred in 31.5% of them. This incidence is higher than that observed in a previous study conducted in Morocco (10.0%) (22).

Table 2. Univariate and multivariate logistic regression analysis of participants characteristics by ADRs occurrence status

Variables	ADRs occurrence		Univariate analysis OR (95% CI)	P-value	Multivariate analysis OR (95% CI)	P-value
	Yes	No				
	n (%)	n (%)				
Age ≤ 40						
Yes	15(37.50)	53(50.96)	0.690 (0.390-1.22)	0.101	0.556 (0.236-1.31)	0.178
No	25(62.50)	51(49.04)	1			
Gender						
Female	22(55.00)	38(36.54)	0.611 (0.390-0.804)	0.049	2.214 (1.041-4.635)	0.046
Male	18(45.00)	66(63.46)	1			
Health insurance						
Yes	34(85.00)	78(75.00)	0.933 (0.558-1.56)	0.793		
No	06(15.00)	26(25.00)	1			
Residence						
Urban	35(87.50)	98(94.24)	0.758 (0.451-1.27)	0.295		
Rural	05(12.50)	06(5.76)	1			
Addiction						
Yes	10(25.00)	44(42.31)	0.568 (0.332-0.970)	0.038	3.358 (1.478-8.419)	0.019
No	30(75.00)	60(57.69)	1			
HIV						
Yes	03(7.50)	05(4.81)	0.639 (0.279-0.714)	0.193	1.605 (0.365-7.055)	0.531
No	37(92.50)	99(95.19)	1			
Comorbidities						
Yes	13(32.50)	45(43.27)	0.595 (0.351-1.01)	0.153	1.309 (0.626-2.737)	0.474
No	27(67.50)	59(56.73)	1			
Type of TB						
PTB	36(90.00)	61(58.65)	0.735 (0.439-1.23)	0.243		
EPTB	04(10.00)	43(41.35)	1			
Previous TB history						
Yes	05(12.50)	21(20.19)	0.686 (0.408-1.15)	0.145	1.565 (0.541-4.520)	0.408
No	35(87.50)	83(79.81)	1			

The occurrence of ADRs varies widely around the world. Some studies have found low proportions compared to ours, with 3.43% in Turkey, 15.08% in China, and 26% in Rwanda (7,14,23). Whereas others have reported high proportions of 41.5%, 59.89, and 65.7% in Brazil, Iran, and Russia, respectively (8, 24, 25).

Gastrointestinal symptoms were the most common ADRs observed in our series and several other searches (23,24). Cutaneous manifestations were the second ADR most noted in our patients. In the literature, the impact of this symptom differs from one study to another, with 5.7% found by Tan et al and 21% by Ravichandran et al (26,27). Regarding hepatotoxicity, the third secondary effect in our series, it has been shown that anti-tuberculosis drugs are one of the most common groups responsible for this manifestation (28). Overall, hepatotoxicity attributed to anti-tuberculosis drugs has been reported in 5% to 28% of patients treated with anti-tuberculosis drugs (29). These varying incidence rates are influenced by the drug regimens involved, monitoring, and reporting practices (28).

Various factors are associated with anti-tuberculosis drugs ADRs, including patient age, malnutrition, the presence of pre-existing diseases, co-infection with the human immunodeficiency virus (HIV), and alcoholism (7,8). Our results showed that patients with addictive habits have a significant risk of experiencing ADRs. Indeed, these toxic products contribute to the occurrence of ADRs by

weakening the immune system, which makes individuals more susceptible to infections. Moreover, they can alter the body's ability to metabolize anti-tuberculosis drugs, leading to the onset of ADRs (30). Our findings showed that women experienced more frequent ADRs compared to male, despite having equal access to healthcare in our context. This may be explained by metabolic, genetic, or hormonal differences between the two sexes. Patient outcomes showed that cases successfully treated were 64.58%, below the WHO target of 85% (31). However, the loss to follow-up in our series (2.08%) was low compared with a previous Moroccan study reporting rates of 14.3% (22).

This study of the adverse effects of anti-tuberculosis drugs, and the risk factors influencing their occurrence, sheds light on an interesting aspect of public health, namely the safety of these treatments in the context of a middle-income country like Morocco. One of the strong points of our study is its originality and exhaustive nature. Indeed, we worked on a sample of a significant size with an extensive review of patients' medical records. Nevertheless, some limits of this study should be mentioned, mainly its retrospective design that limited our capacity to access critical data such as which drug is specifically associated with more side effects and concomitant medications that may influence the onset of these effects.

CONCLUSION

Although anti-tuberculosis treatment is crucial to fighting tuberculosis, it can be associated with a variety of ADRs, ranging from skin reactions to liver damage, which can progress to more severe complications. Close medical monitoring and a collaborative approach between healthcare professionals and patients are essential to minimize risks while ensuring effective tuberculosis control. Continued research into identifying and managing adverse drug reactions is imperative to enhance patient safety and treatment outcomes in tuberculosis management.

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