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Research Article

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Hepatotoxicity of Anti-tuberculosis

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ABSTRACT

Tuberculosis remains a major public health problem despite the implementation of many strategies from fight, essentially based on antituberculosis treatment. However, these drugs can cause quite common side effects include potentially serious hepatotoxicity, often posing a management problem. To assess this complication of Antituberculosis treatment, we conducted a descriptive retrospective study of 80 cases of hepatotoxicity, listed by the Pharmacovigilance Unit of department Pharmacology-toxicology in UHC Ibn Rochd of Casablanca for the past seven years from January 2008 to December 2014. Hepatotoxicity represented 10% (80 cases) of all notifications of adverse drug reactions. The middle age of patients was 28 years, with a female predominance and a sex ratio W/M of 1,74. 75% of patients were under the combination of four antituberculosis drugs (RHZE); 32.5% were taking other drugs associated with antituberculosis regimen can be increased the risk of occurrence of this EIM. 2/3 of the patients had a period of occurrence of hepatotoxicity between 1 and 20 days. The clinical and biological profile most predominant was the cytolytic hepatitis (50%). The interruption of treatment was recommended in (88.75%). Regression of hepatotoxicity was observed in 80% of patients after antituberculosis treatment stop. The evolution was favorable in 40% of cases. The establishment of well codified recommendations is necessary to minimize the risk of occurrence of this adverse effect by enabling better tolerance and compliance.

Keywords: Hepatotoxicity; Antituberculosis drugs; Recommandations; Prevention; Readministration protocol

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INTRODUCTION

Tuberculosis is a main public health problem in the world. In 2013, the World Health Organization (WHO) estimated the number of new Tuberculosis cases to 9 M [1-2]. In Morocco, its frequency remains higher with 27000 to 28000 new cases detected every year, that is an incidence of 83 cases for 100000 inhabitant [3]. That is why; many strategies have been set on, based mainly on a well-standardized tuberculosis treatment, involving four main first-line antibiotics: isoniazid (INH), rifampicin (RMP), pyrazinamide (PZA) and ethambutol (EMB). However, they can cause quite common side effects including potentially serious hepatotoxicity, requiring management and monitoring when starting the treatment [4]. Throughout our study, we will try to show hepatotoxicity antituberculous' frequency through case reports collected in Ibn Rochd University Hospital by the pharmacovigilance department, where it is placed among drug side effects, the most common clinical forms, associated risks factors and the different management models to develop some recommendations for prevention.

MATEREILS AND METHODS

We led a retrospective descriptive study, based on files collected by the functional unit of Pharmacology-Toxicology department of UHC Ibn Rochd Casablanca over a period of 7 years (from January 2008 to December 2014).

Inclusion criteria

tuberculous patients of antituberculosis treatment, on protocols as defined by the national program against tuberculosis and who developed hepatic affection over the period studied.

Exclusion criteria

Patients who developed liver toxicity before starting antituberculosis treatment or who developed hepatotoxicity on another medication;

Data collection was based on a paper sheet with the various pharmacovigilance parameters.
Data entry was made on the EPI INFO version 3.5 software, while processing and statistical analysis were performed using SPSS Version 20 software.

RESULTS

Frequency

During the past seven years (2008-2014), the Pharmacovigilance Unit of Pharmacology department received 80 hepatotoxicity notifications of antituberculosis treatment, with a frequency of 10% compared to other adverse drug reactions collected by the department.
The highest rates of notifications were seen in 2010 with a rate of 23.75% and on 2008: 22.50% (Figure 1).

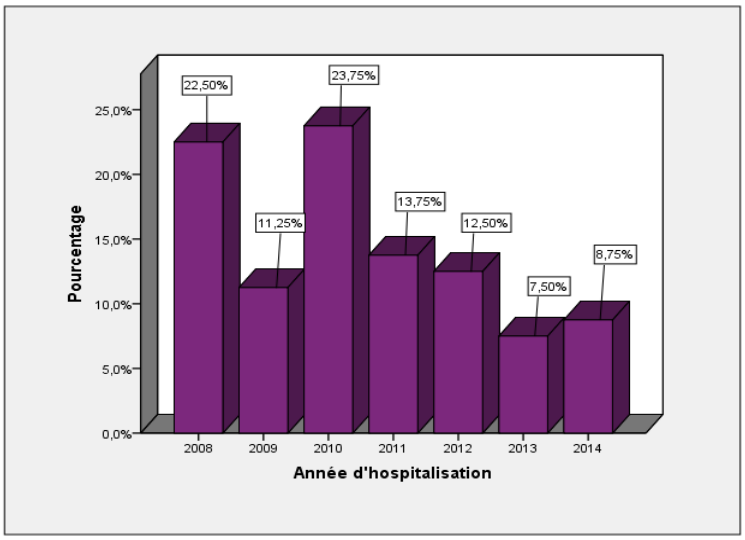

Figure 1: Hepatotoxicity Distribution based on hospitalization years

Age

Most of our patients had an age between 20 and 30 years, that is 32.50% of the cases (Figure 2), with an average age of 28 years.

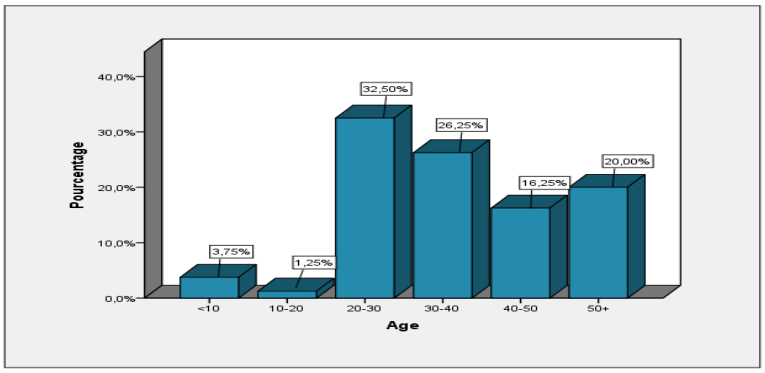

Figure 2: Distribution of patients by age

Gender

There was female predominance: 51 womens (63.1%) versus 29 mens (36.3%) with female / male sex ratio of 1.74 (Figure 3).

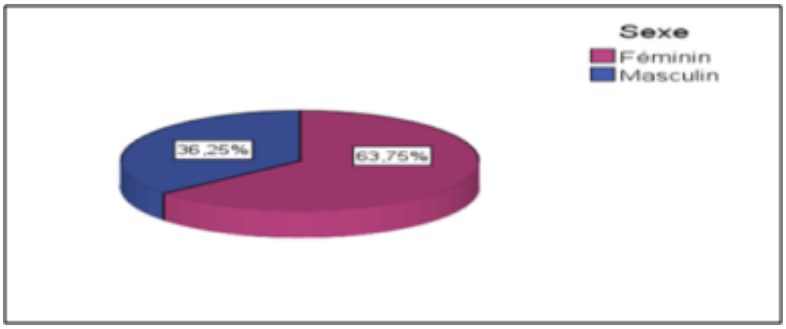

Figure 3: patients Distribution by gender

Background

- -Most of our patients had no previous pathological history
- -Three Patients (3.75%) had confirmed viral hepatitis B
- -Six patients (7.5%) were known HIV positive +++
- -Ten Patients (12.5%) experienced taking medicines:
  - Two patients were taking paracetamol alone or with ibuprofen
  - A woman used oral contraceptives.
  - The other patients taking other drugs: antibiotics, AVK, steroids and cardiovascular drugs
- Eighteen patients (22.5%) had toxic history: alcohol, smoking, herbs, drugs or a combination
- Fourteen patients (17.5%) reported to have tuberculous contagion history

Tuberculosis type

Disseminated tuberculosis was the most common, and shows out in 20% of the patients, followed by peritoneal and pulmonary tuberculosis with equal proportions.

Treatment

In our series, most of the patients (75%) were on four antiTuberculosis treatment: INH / RPM / PZA / EHT or streptomycin, while 21.25% were on 3 antiTuberculosis (INH / RPM / PZA or EHT) and the left patients on 2 antiTuberculosis (INH / RPM) **(**Figure 4), 26 patients (32.5%) were on other drugs associated with antiTuberculosis treatment: beta-lactams antibiotics, sulpha antibiotics and antifungals, paracetamol, AVK, beta-blockers, fluoroquinolones, antiepileptics, IPP, and antiretrovirals.

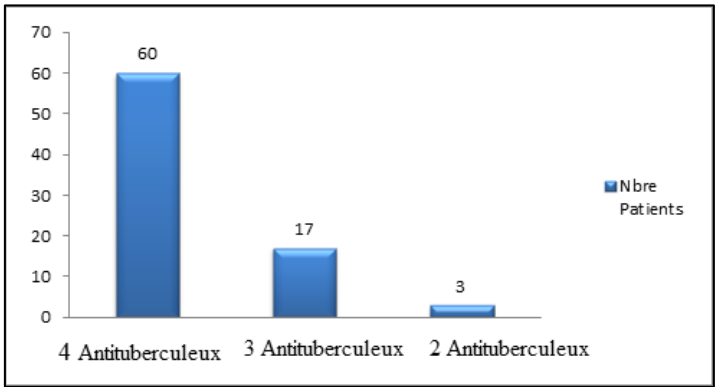

Figure 4: Cases Distribution according to the number of tuberculosis drugs administered

Onset time

The Time between antituberculous treatment beginning and the onset of hepathic affection ranged from 1 to 165 days. In most of our patients (66.25%), the time was between 1 and 20 days. The time of side effect onset was suggestive in nature in 90% of the cases and compatible in 10 %.

Discovery circumstances
In 38 patients (47.5 %), the hepatotoxicity discovery was asymptomatic, incidentally revealed by hepatic disturbances (increased transaminases).

Associated clinical signs
Health impairment was the most noted sign (37.5%), followed by jaundice (23.75%) and dyspeptic syndrome (22.5%) involving nausea, vomiting and abdominal pain.

Biological assessment
ALAT rate was below 3 N in 13.75% of the patients and greater than or equal to 3N in 86.25% of the patients, including 23 patients (28.75%) had a higher rate to 10N (Table 1). PAL rates ranged from less than 2N (63.75%) and 2N (15%) (Table 2).

Table 1: Cases distribution according to ALAT's rates

ALAT rates	Patients N (%)
<3N	11 (13.75)
3-5N	21 (26.25)
5-10N	25 (31.25)
>10 23	23 (28.75)
Total	80 (100)

Table 2: Cases distribution according to PAL's rates

PAL rates	Patients N (%)
<2N	51 (63.75)
<2N	12 (15)
2N	6 (7.5)
N	3 (3.75)
NA	8 (10)
Total	80 (100)

The γGT was increased in 43.8 % of the patients
- Total Bilirubine in 29 %
-TP was performed in 32.5 % of the patients and decreased in 14 of them
- Haemogram Was normal in most of the patients with hyper eosinophilia noticed in three patients
- Viral serology was not performed in most of the patients and underlined one case of viral hepatitis C and seven cases of HIV were positive.
- Autoimmune antibodies were required for 4 patients while autoimmune hepatitis suspected but revealed negative.

Morphological assessment
Performed in order to eliminate other non-drug causes.
-Abdominal ultrasound was performed in 70 % of the patients and showed:
* cholelithiasis in 2 patients,
* hepatomegaly in 11 patients,
* Hepatic steatosis in 3 patients.
-An Echocardiogram was performed in 7 subjects, one of which revealed a heart defect.

Clinico-biological forms
The cytolytic form (ALAT /PAL) was the most predominant : noted in 40 patients, (50%) of the cases, followed by mixed hepatitis in 22.50 % and cholestatic hepatitis (17.50%) (Figure 5); Hepatotoxicity Severity according to WHO classification (based on ALAT levels) were: mild in 32 patients (40%), moderate in 25 patients (31.25%), while 23 patients (28 75%) developed a severe form.

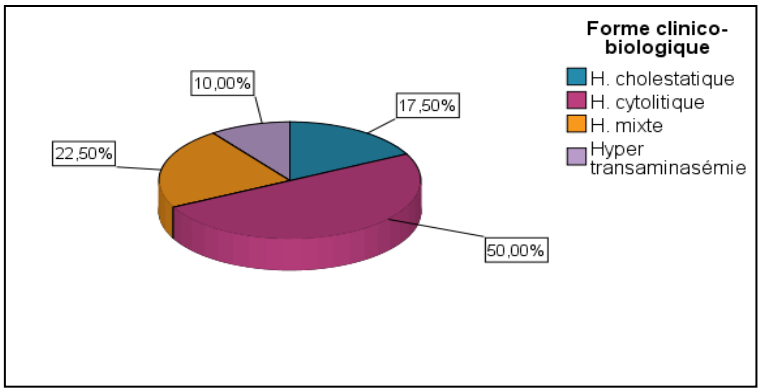

Figure 5: cases distribution according to clinicobiologic form

Hospitalization's management

- Stopping antituberculous treatment was recommended in 88.75% of the cases. Two patients (2.5%) received dose treatment adjustment, six patients (7.5%) continued antituberculous therapy with biological monitoring
- The reintroduction was carried out in 17 patients (31.50%)

Course

- Hepatotoxicity Reduced after treatment discontinuation in 80% of the cases
- After treatment's reintroduction, hepatotoxicity recurrence was noticed in 8.75 % of the patients, whereas it was negative in 11.25 %.

Final course was unknown in 57.50% of the patients while 40% have well recovered without sequelae and 2.50 % died.

DISCUSSION

Hepatotoxicity is one of the most frequent and severe side effects of antituberculous during treatment. Its incidence has been reported with a variable rate between 2 and 28% of the patients treated. [5] It may be responsible for 6 to 12% mortality if treatment is continued [4]. It predominates for the three basic antibacillaries (isoniazid [INH], pyrazinamide [PZA] and rifampicin [RPM]) which association is almost constant in different treatment regimens, however the concomitant administration increases the hepatotoxicity's incidence and makes hepatic affection most serious [4]. Indeed, isoniazid produces toxic metabolites by cytochromes P45O (hydrazine +++) [6], RMP interacts potentially with hepatic microsomal system (CYP 450) and is a great metabolism inducer of several drugs including the isoniazid [6,7], as for pyrazinamide toxicity is less frequent, but more serious and later of immunoallergic origin, and ethambutol and streptomycin induce only very rarely hepatotoxicity by immunoallergic mechanism [6]. In Morocco, hepatic toxicity on antituberculous treatment is quite common, given the endemic nature of tuberculosis and slow acetylator genetic profile of our population. Many risk factors have been identified as predisposing to antituberculous hepatic toxicity: advanced age, female gender, viral infections (HIV +++, HVB, HCV), alcohol, high doses, long term treatment, concomitant use of hepatotoxic agents and the genetic polymorphism of enzymes (NAT2 genotypes, CYP2E1) [8,9].

In our series tuberculosis affects mainly young subjects between 20-40 years (58.75%), female (63.1%), most of our patients had no pathological history, except three patients (3, 75%) who had a viral hepatitis B, six patients (7.5%) were known positive HIV +++, ten patients (12.5%) had earlier drug intake and eighteen patients (22.5%) had a history of toxic use: alcohol, smoking, medicinal plants, drugs or a combination of several.

The time of hepatotoxity onset in our series joins that of literature [10,11].

Table 3: Hepatotoxicity onset Time according to several studies

Authors	Délai (j)	Percentage %
Assob et al.	31	69 ,23
Senaratne et al.	30	58
Mahmood et al.	14	61
Notre série	20	66,3

Hepatotoxicity is asymptomatic in most of the cases accidentally revealed by biological assessement disturbances or associated with nonspecific signs including nausea, vomiting, asthenia, anorexia, abdominal pain or jaundice [5].

Cytolytic acute hepatitis is the most common form, mainly induced by isoniazid and pyrazinamide. [12] Fadlouallah M. and al reported cytolytic affection in 47.5% of the cases [13], for E.Benjazia and al cytolytic affection was noted in 84% of the cases [14]. Similarly, hepatotoxicity severity was variable depending on several series: Haji Khan Khoharo and al have reported lesser hepatotoxicity, moderate and severe in 48 (52.75%), 40 (43.95%) and 3 (3 3%) cases, respectively [15]. Our results were consistent with the literature, where cytolytic hepatitis was 50% of the cases as mild (40%) and moderate (31.25%).

Learning societies, BTS (British Thoracic Society), ATS (American Thoracic Society) and ERS (European Respiratory Society), recommended in case of moderate or severe hepatotoxicity with transaminase levels> 5 times normal or> 3 times normal with hepatotoxicity symptoms, immediate discontinuation of antituberculous treatment until normalization of liver function, if tuberculosis affection is severe and requires treatment continuation, other -therapeutic alternatives non hepatotoxic could be used: the streptomycin and the fluoroquinolones.

The re-introduction is recommended after normalization of liver function, however, several models have been suggested in the literature, based mainly on the re-introduction of the least hepatotoxic molecule, gradually increasing the dose with careful clinical and biological monitoring of safety.

The readministration protocol according to BTS [16]
After normalization of liver function, the reintroduction is done in the following order: INH, RMP and then PZA, with daily monitoring of the patient's clinical status and his hepatic function. L'INH should be initially introduced at 50 mg / day, by sequentially increasing to 300 mg / day after 2-3 days if no reaction occurred; followed by the RPM at a dose of 75 mg / day and 300 mg after 2 to 3 days, then 450 mg (if weight <50 kg) to 600 mg (if> 50 kg). Finally, PZA is introduced at 250 mg / day and 1.0 g after 2-3 days and then 1.5 g (if the weight <50 kg) or 2 g (if> 50 kg).

Readministration according to ATS: [17]
RMP is reintroduced with or without EHT after ALAT decrease of at least twice the upper limit to normal, then followed by readministration of INH, after 3 to 7 days. In case of symptoms recurrence or ALAT increase, last drug reintroduced should be stopped. For PZA, its reintroduction can be dangerous in case of severe hepatotoxicity.

Such was the case in our series, immediate end p of antituberculous treatment was recommended in 88.75% of the cases, with regression of liver toxicity in 80% of the cases.
readministration was made for 17 patients (31.50%) after normalization of liver function, according to different patterns (ethambutol, rifampicin, pyrazinamide and isoniazid +++) with recurrence of side effects in 8.75% of the patients and negative in 11.25%.

CONCLUSION

Antituberculous hepatotoxicity is an unpredictable effect, potentially severe, therefore requiring adequate management, to allow better tolerance and compliance. In fact, antituberculous treatment is obligatory for tuberculosis management especially in our context where this disease remains endemic with no other therapeutic options. That is why Morocco adopted new means and set on "National Plan of accelerating the reduction of Tuberculosis incidence 2013-2016."

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