ECRONICON OPEN ACCESS

EC GASTROENTEROLOGY AND DIGESTIVE SYSTEM

Retrospective Study

Antibacillary Toxic Hepatitis

S Driouiche*, H Hedda, M Lahlali, A Lamine, N Lahmidani, A Elmekkoui, M ELyoussfi, D Benajah, M ELabkari, A Ibrahimi and H Abid

Department of Hepato-Gastroenterology, CHU HASSAN II - FES, Faculty of Medicine and Pharmacy, Sidi Mohammed Ben Abdellah University, Fez, Morocco

***Corresponding Author:** S Driouiche, Department of Hepato-Gastroenterology, CHU HASSAN II - FES, Faculty of Medicine and Pharmacy, Sidi Mohammed Ben Abdellah University, Fez, Morocco.

Received: January 04, 2023; **Published:** January 16, 2023

Abstract

Introduction: Antibacillary treatment is likely to cause a number of side effects among which toxic hepatitis. The latter can range from a simple transient disturbance of the liver balance to fulminant hepatitis.

Aim of the Study: The aim of our work is to highlight the frequency of hepatotoxicity of anti-bacillary drugs, the severity of certain lesions and the need for a rigorous follow-up for early detection and immediate discontinuation of treatment.

Methodology: This is a retrospective study from January 2012 to August 2021. During this period, 10 cases of patients followed for tuberculosis regardless of its location, hospitalized in our department, for management of acute hepatitis secondary to antituberculosis drugs.

Results: The mean age of our patients was 38 years, with a sex ratio M/F 0.66. The location of the tuberculosis was pulmonary in 4 cases, lymph node in 2 cases, peritoneal in 2 cases, pleural in 1 case and mammary in 1 case. The discovery of hepatotoxicity was made in 10 cases at the onset of clinical manifestations. All our patients were under anti-tuberculosis treatment combining rifampicin, isoniazid, pyrazinamide and ethambutol. There was no associated drug use. All patients had a correct initial liver function test but without a surveillance liver test during the course of the antituberculosis treatment. After an average of 60 days, the patients presented a frank cutaneous-mucosal jaundice followed by signs of hepatic encephalopathy up to coma in 1 case. The hepatic workup showed a cytolytic hepatitis with a cytolysis superior to 10 times the normal. The mean value of prothrombin level was 44% [13-94%]. The etiological workup for a cause other than drugs was negative. The anti-tuberculosis treatment was stopped in all patients. The evolution was favorable in 8 patients with clinico-biological improvement. On the other hand, one patient presented a relapse in the form of a non severe acute hepatitis after progressive reintroduction of the antituberculosis treatment and one patient died at day 5 of his hospitalization.

Conclusion: Antibacillary toxic hepatitis can compromise the patient's vital prognosis hence the need for rigorous monitoring to detect and manage possible side effects as early as possible.

Keywords: *Antibacillary Drugs; Hepatotoxicity of Variable Severity; Cytolytic Hepatitis; Treatment Discontinuation*

Introduction

Tuberculosis is a public health problem worldwide. Tuberculosis treatment is longer and involves several drugs that can induce hepatotoxicity, which can range from a simple transient disturbance of liver function tests to fulminant hepatitis.

Objective of the Study

Objective of our work is to highlight the frequency of antibacillary hepatotoxicity and the severity of certain lesions.

Patients and Methods

This is a descriptive retrospective study from January 2012 to August 2021. During this period, 10 cases of patients followed for tuberculosis regardless of its location, hospitalized in our department, for management of secondary acute hepatitis to anti-tuberculosis drugs.

Results

The average age of our patients was 38 years [57 - 21], with a sex ratio M/F 0.66. The localization of tuberculosis was pulmonary in 4 cases, lymph node in 2 cases, peritoneal in 2 cases, pleural in 1 case and mammary in 1 case. The discovery of hepatotoxicity was made in 10 cases after the onset of clinical manifestations. All our patients were on antituberculosis treatment combining rifampicin, isoniazid, pyrazinamide and ethambutol. No associated drug intake was noted. All the patients had a correct initial hepatic test, but without hepatic test monitoring during the antituberculosis treatment. The patients presented, after an average delay of 2 months [1 - 5 months], frank mucocutaneous jaundice followed by signs of hepatic encephalopathy up to coma in 1 case. The liver test showed cytolytic hepatitis with cytolysis greater than 10 times normal. The mean prothrombin level value was 44% [13 - 94%]. The etiological assessment in search of a cause, other than drug, was negative. Antituberculous treatment was stopped in all patients. The evolution was favorable in 8 patients with clinical and biological improvement. In addition, one patient presented a relapse in the form of non-serious acute hepatitis after gradual reintroduction of anti-tuberculosis treatment and one patient died on day 5 of his hospitalization.

The results of the clinical and paraclinical study are illustrated in table 1.

Parameters	N (%)
Mean age	38 years
Sex ratio M/F	0,66
Tuberculosis locations	- Pulmonary N = 4 (40%) - Lymph node N = 2 (20%) - Peritoneal N = 2 (20%) - Pleural N = 1 (10%) - Mammary N = 1 (10%)
Type of antibacillary treatment	- Rifampicin, Isoniazid, Pyrazinamide, Ethambutol
Average time to clinical manifestation	- 2 months [1 - 5 months]
Clinical presentation	- Mucocutaneous jaundice N = 10 (100%) - Hepatic encephalopathy N = 1 (10%)
Initial hepatic workup	- Normal N = 10 (100%)
Clinical-biological monitoring during antibacillary treatment	- Not done N = 10 (100%)

Biological presentations	- Cytolytic hepatitis N = 8 (80%) -Cholestatic hepatitis N = 2 (20%)
Cytolysis values	- Greater than 10 times normal N = 10 (100%)
Mean values of prothrombin level	- 44% [13 - 94%]
Etiological tests	- Ultrasound: Normal N = 5 (50%) Chronic hapatopathy liver N = 2 (20%) Hepatic cirrhosis N = 1 (10%) Hepatic steatosis N = 1 (10%) Budd Chiari syndrome N = 1 (10%) -Viral serology N = 10 (100%) - EPP N = 10(100%) - Autoimmune test 1 and 2 intention N = 10 (100%) - Wilson's disease test N = 5 (50%) - Liver biopsy N = 6 (60%)
Results of etiological tests	- Normal viral serology N = 10 (100%) - EPP: Hypegamma a 1,5 times normal N = 4 (40%) - Positive anti nuclear ac N = 2 (20%) M2 type anti-motochondrial CA + N = 2 (20%) - PBH: Chronic liver disease N = 6 (60%)

Table 1: *General characteristics of our patients.*

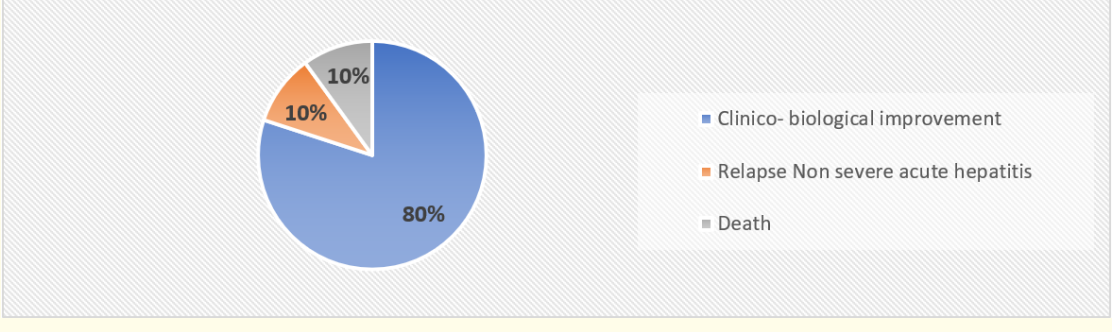

Figure 1: *Evolution of our patients after stopping antibacillary treatment.*

Discussion

Tuberculosis remains a major public health issue worldwide. Antibacillary treatment based essentially on isoniazid (INH), pyrazinamide (PZA), rifampicin (RPM), used in combination and for a prolonged period according to different protocols, can be responsible for numerous side effects, including toxic hepatitis.

Isoniazid is a classic provider of cytolytic hepatitis requiring discontinuation in 1% of treated patients [1]. The mechanism is idiosyncratic. The slow acetylator phenotype is associated with reduced detoxification of acetylhydrazine and other hepatotoxic metabolites. Other factors are also favoring the occurrence of toxic hepatitis: co-treatment with rifampicin, consumption of ethanol and advanced age.

our study and also in the series of K. Chaanoun., *et al*. [2], the average age was 38 years. These results are lower than those reported by many authors who found an average age of 45 years [3-5].

Rifampicin is responsible for a moderate and early increase in transaminases, most often associated with 0.3 to 0.4% jaundice [6]. RMP often determines cholestatic hepatitis by competition with bilirubin [7]. Only RMP is rarely hepatotoxic, in combination with INH it induces the formation of reactive and unstable metabolites of INH, thus increasing its hepatotoxicity and reducing the time to onset.

Pyrazinamide, its liver toxicity is less frequent, it is more serious, later, and it is dose-dependent [8]. Its frequency is estimated between 0.5 and 10% of symptomatic hepatitis according to studies and drug associations. Cytolytic hepatitis is the most common [9]; moreover, it may be a simple elevation of transaminases; finally, a case of granulomatous hepatitis following the administration of PZA has been reported [10].

Ethambutol Its liver toxicity is rare, it is most often a simple moderate hyperbilirubinemia without jaundice, discovered on the liver test and not requiring the cessation of treatment. Exceptionally, true cholestatic liver damage has been described which remains reversible on discontinuation of treatment. The mechanism of hepatotoxicity is immunoallergic, with a time to onset between four days and two months [11]. Streptomycin its hepatotoxicity is exceptional, due to an immunoallergic mechanism [11].

A distinction is made between pulmonary tuberculosis and extra-pulmonary tuberculosis. Belgian data show that pulmonary tuberculosis was the most frequent form (70 to 75% of cases) against 30% for extra-pulmonary tuberculosis and 8.5% for mixed forms [12].

The predominance of the pulmonary localization was observed in all the series [2-5], which also joins our series on the other hand the mode of revelation hepatotoxicity differs, in our series was noted following the onset of clinical manifestations in 100% of cases, however in the series H. Beggar and Al [4], W. Jalloul and Al [5]; one third of cases of hepatotoxicity was revealed during periodic monitoring liver function tests before the onset of clinical manifestations.

The patients presented, after an average period of 02 months [01 - 05 months], clinical manifestations of hepatotoxicity, which are consistent with the data in the literature.

On the lesional level, hepatic damage secondary to anti-tuberculosis drugs can be acute or become chronic as a result of polymorphic clinical and biological pictures (Table 2).

	Number of bibliographical references	Biological hepatitis	Cytolytic hepatitis	Cholestatic hepatitis	Hepatitis acute	Hepatitis massive	Chronic lesions
INH	193	66	86	12	119	46	Chronic hepatitis = 3 Cirrhosis = 4 Steatosis = 1 Granulomatous = 1
RMP	69	25	18	20	44	6	-
ZAP	104	25	69	9	89	30	Chronic hepatitis = 1 Granulomatose = 1
ETA	24	11	7	6	15	2	-
OGE	9	1	2	2	8	0	-
SMY	5	1	3	1	5	1	-
INH: Isoniazid; PZA: Pyrazinamid; RMP: Rifampicin; ETA: Ethionamid; EMB: Ethambutol; SMY: Streptomycin							

Table 2: *Hepatotoxicity of anti-tuberculosis drugs.*

Cytolytic hepatitis is the most frequent form, mainly induced by INH and PZA. Its clinical expression depends on hepatocyte damage.

It can be asymptomatic with an isolated increase in transaminases or can be revealed by specific symptoms such as: anorexia, nausea, vomiting and abdominal pain. Jaundice is a more advanced stage of hepatocyte necrosis. Massive necrosis results in hepatic encephalopathy with flapping, confusion and coma. The underlying physiopathological mechanism is direct by the excessive formation of hepatotoxic metabolites (N-acetyl INH), induced especially by the RPM-INH association.

In our series and also in other series [2-5], we noted a predominance of the cytolytic form of toxic liver damage.

Discontinuation of the anti-tuberculosis drug is usually followed by clinical improvement with normalization of liver tests in the order of a few weeks, which was observed in our series in almost all cases and also in the other series [2-5].

After normalization of liver function tests, the reintroduction of treatment will be done starting with the least hepatotoxic drugs, i.e. ethambutol and/or streptomycin, followed by the introduction of the rest of the drugs at least or more. suspicious, depending on the chronological and semiological context (RMP, INH, PZA), with close monitoring of liver function tests. The pace of reintroduction should be gradual. If during the reintroduction of one of the drugs there is a disturbance of the liver balance sheet, it must be stopped definitively [13,14].

If reintroduction is impossible, the introduction of replacement drugs is recommended, in particular fluoroquinolones, ethambutol, cycloserine [15].

The management of hepatotoxicity with antibacillary drugs is essentially based on prevention, which must obey certain rules:

- Screening of the population at risk;
- Patient education;
- Clinical and biological monitoring during treatment and the use of plasma monitoring;
- The declaration to the pharmacovigilance center of cases of hepatitis to anti-tuberculosis drugs remains the only means of evaluating the incidence of this complication and also makes it possible to assess the tolerance of the population to anti-tuberculosis drugs.

Unfortunately, in our population, we have a failure on this level; hence the finding of high levels of hepatotoxicity to antibacillary drugs in comparison with other countries.

Conclusion

In the literature; in most cases, antibacillary hepatotoxicity has been associated with advanced age and pre-existing liver damage; something that was not objectified in our study and also in most of the series, which makes it necessary to think about the acetylation profile of Moroccan patients (slow and intermediate acetylators), hence the interest of the plasma dosage of antibacillary drugs, making it possible to detect high concentrations of INH and the individual adjustment of dosages according to the terrain and of the acetylation profile and without forgetting to establish close clinical and biological monitoring (hepatic enzymes, prothrombin level).

Bibliography

1. Lee WM. "Acute liver failure in the United States". *Seminars in Liver Disease* 23 (2003): 217-226.
2. K Chaanoun., *et al*. "Hépatotoxicité aux antituberculeux: à propos de 15 cas". *Revue des Maladies Respiratoires* 35 (2018): A270-A271.

3. Fadlouallah., *et al*. "Hépatite toxique aux antibacillaires: à propos de 79 cas". *JFOHD* (2009).

4. H Beggar., *et al*. "Hépatite toxique aux antibacillaires: à propos de 98 cas". *JFOHD* (2017).

5. W Jalloul., *et al*. "Hépatotoxicité aux antituberculeux: à propos de 19 cas". *Revue des Maladies Respiratoires Actualités* 13.1 (2021): 211.

6. El Ftouh M., *et al*. "Médicaments antituberculeux: effets secondaires et conduite à tenir". *Médecine du Maghreb* 67 (1998): 35-38.

7. Kshirsagar A., *et al*. "Drug induced hepatotoxicity: a comprehensive review". *The Internet Journal of Pharmacology* 8 (2010): 2.

8. Durand F., *et al*. "Deleterious influence of pyrazinamide of the outcome of patients with fulminant: subfulminant liver failure during tuberculosis treatment including isoniazid". *Hepatology* 21.4 (1995): 929-932.

9. Aouam K., *et al*. "Les effets indésirables des antituberculeux: épidémiologie, mécanismes et conduite à tenir". *Médecine et Maladies Infectieuses* 37 (2007): 253-261.

10. Knobel B., *et al*. "Pyrazinamidinduced granulomatosis hepatitis". *Journal of Clinical Gastroenterology* 24.4 (1997): 264-266.

11. Ben Salem C and Chazouillères O. "Hépatotoxicité des médicaments 14e mise à jour du fichier bibliographique des atteintes hépatiques et des médicaments responsables". *Gastroentérologie Clinique et Biologique* 28 (2004): 720-759.

12. K Chaanoun., *et al*. "Hépatotoxicité aux antituberculeux: à propos de 15 cas". *Revue des Maladies Respiratoires* 35 (2018): A270-A271.

13. Abaakil H. "Hépatopathies médicamenteuses". Thèse de doctorat en médecine, Casablanca (2007): no83.

14. Tahooqlu K. "The management of antituberculosis drug induced hepatotoxicity". *The International Journal of Tuberculosis and Lung Disease* 5.1 (2001): 65-69.

15. An official ATS statement: hepatotoxicity of antituberculosis therapy. *American Journal of Respiratory and Critical Care Medicine* 174 (2006): 935-952.

Volume 10 Issue 1 January 2023