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Research paper

Hepatotoxicity during anti tuberculosis chemotherapy

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Abstract

Introduction: Despite their efficacy in tuberculosis treatment, side-effects of anti-tuberculosis drugs can be serious or fatal. The aim of our study is to determine the prevalence of hepatic toxicities associated with anti-tuberculosis drugs, their evolutionary aspects, and their management.
Patients and methods: A retrospective descriptive study including 82 patients having received antituberculosis treatment and who presented a hepatic cytolysis, collected at the Tuberculosis and Respiratory Diseases Control Department of Batna- Algeria between 2016 - 2023. The aim of our study is to determine the prevalence of hepatic toxicities of anti-tuberculosis drugs, their evolutionary aspects, as well as the modalities of their management.
Results: 82 out of 119 (69.23%) patients who experienced other adverse events were recruited between 2016 and 2023, aged between 15 and 86 years, with an average age of 43 years and a female predominance of 63.41%. Cholestasis syndrome was noted in 21 patients and frank jaundice in 4. Cytolysis was discovered incidentally in 68% of patients; it was mild in 56 (68.29%), moderate in 16 (19.51%) and severe in 10 (12.19%). Transaminase disturbance appeared within 3 months in 76.82% of cases, whereas a delay of 30 days was noted for normalisation of the liver function test after cessation of anti-tuberculosis treatment in 62 (76%) patients. Definitive discontin-uation of isoniazid (INH) was adopted in 17 (20%) patients, while a reduction in the doses of rifampicin and isoniazid was decided in 65 (80%) patients.
Conclusion: Drug-induced hepatitis is one of the major side-effects of anti-tuberculosis drugs and can be lethal, hence the need for rapid and appropriate management. Healthcare professionals need to be informed about the types of suspected adverse drug reactions, they should report in subjects at risk.

Keywords: *Tuberculosis; Adverse Reactions; Anti-Tuberculosis Treatment; Cytolysis; Cholestasis; Isoniazid.*

1. Introduction

The occurrence of several adverse effects inherent in anti-tubercular drugs is possible, and hepatotoxicity is considered a major accident that can be fatal to the patients. Identifying the drug responsible and establishing a practical approach to this clinical situation is an important step in the management of these patients.

2. Patients and methods

This is a descriptive, retrospective, monocentric study, enrolled tuberculosis patients followed up at the Tuberculosis and Respiratory Diseases Control Department of Batna Algeria between 2016 -2023, who developed anti-tubercular drug-induced liver injury. The study looked at the following parameters: socio-demographic information, clinical signs, time to onset of cytolysis, changes in liver function test after treatment cessation and, the management of these patients.

3. Results

Table 1: Patients' Characteristics

Parameters	Résults
Age (years)	43 (15-86)
Sex M : F	30 : 52
Comorbidities	Diabetes : 10 High blood pressure : 03 Other : 14
Localization of tuberculosis	Chest :10 Lymph node : 36 (53%)

	Urinary : 07 Other : 31

Table 2: Discovery Circumstances

Discovery circumstances	Digestive tract signs	Asymptomatique
	32%	68%

Table 3: Liver Function Tests

Parameters	Results		
Hepatic Cytolysis	Mild	ASAT level < 5 times normal	56 (68,29%)
	Moderate	ASAT level : 5-10 times normal	16 (19,51%)
	Severe	ASAT level <10 times normal	10 (12,19%)
Cholestasis	21		
Jaundice	4		

Table 4: Cytolysis Onset Times

0-15 days	15-30 days	1-2 months	2-3 months	03-4 months	05- 6 months	11months
12	19	17	15	10	7	2

Table 5: Time Taken for Liver Function Tests to Return to Normal After Stopping Anti-Tuberculosis Treatment

0-15 days	15-30 days	>30 days
12 (14%)	8 (10%)	62(76%)

Table 6: Final Treatment Plans Adopted

Permanent cessation of isoniazid	Minimal doses of isoniazid and rifampicin
17 (20%)	65 (80%)

4. Discussion

Drug-induced liver injury is a group of anatomical abnormalities secondary to the administration of drugs. It presents in three forms: cholestatic, cytolytic or mixed. However, the incriminating mechanism is either overdose, the formation of a toxic metabolite or an immunoallergic phenomenon.

Isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin are essential antitubercular drugs and may be responsible for several adverse effects: digestive, allergic, ophthalmic, neurological, etc. [1].

In our series, hepatic cytolysis was present in 69.23% of the 119 patients who presented various adverse reactions to antituberculosis treatment, with a predominance of 63.41% among women. On the other hand, in a Tunisian study [2], the prevalence of hepatic cytolysis was 50%, with a predominance of 90% among men. In the USA, hepatotoxicity due to anti-tuberculosis drugs predominates in 20% of cases [3], [4].

Hepatic cytolysis was asymptomatic in 67% of cases in our series, occurring during the first 3 months of antituberculosis treatment in 77% of cases, corroborating the data in the literature [5-7].

Patients in our series developed mild liver damage (serum ASAT levels less than five times normal) in 68.29% of cases, moderate (serum ASAT levels between five and ten times normal) in 19.51% and severe (serum ASAT levels more than ten times normal) in 12.19%. However, from a practical point of view, all anti-tuberculosis drugs should be stopped if transaminase levels exceed five times normal [3], [8]. A cholestasis syndrome and frank jaundice have been observed in 25% and 5% of patients respectively. It is recognised that cytolysis is essentially due to isoniazid and to pyrazinamide whereas rifampicin usually caused cholestasis [9].

In a cohort study [10], an increase in hepatotoxicity rates was observed in women (OR, 3.30; P=0.07) and whites (OR, 2.60 ; P=0.08), the same results were confirmed by another more recent cohort study [11] which found that hepatotoxicity induced by anti-tuberculosis drugs was more often found in younger patients (p = 0.368, OR 2.75), of the female sex (p = 0.219, OR 4.2).

In our series, treatment was stopped until the liver function was normalized, then minimum doses of isoniazid and rifampicin were reintroduced in accordance with national [12] and international (3) guidelines.

The time to normalisation of the liver function was more than 30 days in 62% of patients, leading to a prolongation of the anti-tuberculosis treatment period, with a high risk of non-adherence to treatment on the part of patients.

The resumption of cytolysis was noted in 26% of patients despite the reintroduction of minimal doses of isoniazid and rifampicin, leading to the decision to permanently stop isoniazid and to replace isoniazid with ethambutol in 20% of cases [12].

National [12] and international [3], [8] guidelines in the event of hepatic cytolysis secondary to antituberculosis treatment consist of reintroducing treatment after complete normalisation of the liver function, starting with the least hepatotoxic drugs, i.e. ethambutol and/or streptomycin, followed by the introduction of the remaining drugs, from the least to the most suspect, depending on the chronological and semiological context, with close monitoring of the liver function. If, after reintroduction of any of these drugs, there is a disturbance in the liver function, they should be discontinued permanently.

The most incriminating mechanism in liver toxicity is that hydrazide, which is a metabolite of INH, produces reactive or toxic metabolites that bind to and damage cellular macromolecules in the liver [13], [14].

It is also recognised that liver injury induced by isoniazid is increased by the combination of rifampicin and pyrazinamide, which explains the much higher frequency of hepatitis in patients treated daily with rifampicin and isoniazid [15], [16].

Pyrazinamide can also cause liver damage, followed by rifampicin, while ethambutol is exceptionally hepatotoxic. Determining imputability and establishing a practical approach are based on identifying certain data inherent in the drug, the way it is administered and the liver damage itself [9], [6], [17].

However, it is recognised that liver damage secondary to pyrazinamide is a dreaded adverse effect given its potentially deleterious course [1], [18].

5. Conclusion

The major side-effects of anti-tuberculosis treatment are frequent and serious, dominated by hepatic accidents, which require prolonged management and may lead to discontinuation of treatment, thus necessitating rigorous monitoring.

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