

## **First-line Antituberculosis Drugs. Between the Main Side Effects and their Support. Reported Case and Literature Review**

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### **Abstract**

Tuberculosis is a major public health problem at the global level. In Morocco in 2017, there were 30897 new cases with 9.3% of specific mortality.

The therapeutic regimen of any new form of sensitive tuberculosis in adults without comorbidity is an initial quadritherapy based on the Association of pyrazinamide, ethambutol, rifampicin, and isoniazid.

Therapeutic success requires a good adherence which cannot be achieved without the correct management of the side effects associated with one or more antibacillary drugs, sometimes requiring the adaptation of the therapeutic Protocol.

The objective of this work is to describe the behaviours to be held in front of the main secondary manifestations of first-line antituberculosis drugs, by reporting an observation of drug toxiderma in a particular terrain that necessitated an adaptation of the initial Protocol.

The objective is to maintain an effective therapeutic Protocol to achieve the desired goals according to who, and to eradicate the disease by 2035.

**Keywords:** *Antituberculosis Drugs; Tuberculosis*

### **Introduction**

Tuberculosis is a major public health problem at the global level. In Morocco in 2017, there were 30897 new cases, i.e. 88/100000 inhabitants with 9.3% of specific mortality [1]. According to the national tuberculosis control program (PNLAT), the treatment regimen of any new form of sensitive tuberculosis in adults without associated comorbidity is an initial two-month quadritherapy based on the Association of rifampicin (RPM), isoniazid (INH), pyrazinamide (PZA) and ethambutol (ETB). These first-line antituberculosis drugs can cause adverse reactions that may be life-threatening, which justifies precautions during initiation of treatment and close monitoring [2].

Therapeutic efficacy is a major criterion, and the main target of the PNLAT (national tuberculosis control plan) to achieve the desired objectives. This success cannot be achieved without controlling the harmful effects of anti-tuberculosis drugs in particular first-line medications. A major side effect requires cessation of treatment, which requires looking for an alternative to maintain an effective regimen while evaluating the benefit/risk effect [3].

### **Objective of the Study**

The objective of this work is to describe practical behaviours in the face of major adverse events in front-line antibacillaries, while reporting a drug-related reaction to a patient receiving first which required special care.

**Material and Methods**

This is an observational study of a reported case of drug-induced isoniazid during first-line TB treatment in a particular setting. The patient was initially diagnosed in the visceral surgery department of the Military Hospital Avicenna Marrakech, treated and secondarily in the department of pneumology and Phthisiology of the same hospital.

Subsequently, we have developed practical guidelines for the main adverse events encountered during a first-line anti-tuberculosis treatment.

**Observation**

It is a patient aged 64 years followed for chronic renal failure for 10 years having required three weekly hemodialysis sessions for 2 years following a progression of its renal disease, progressing at the terminal stage with a clearance of creatinine at 9 ml/min/1.73 m<sup>2</sup> SC.

Originally admitted for chronic cough with impaired general condition.

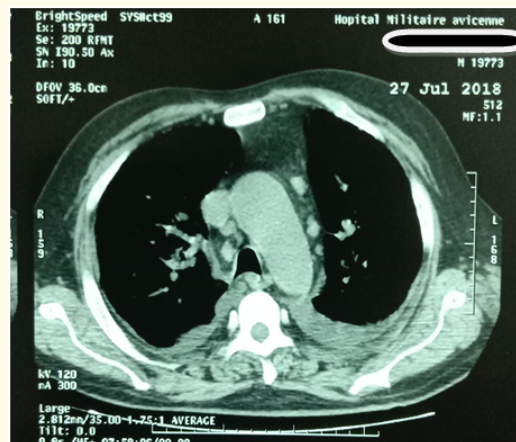
The symptomatology was up to three months by the gradual installation of a nocturnal dry cough with stress dyspnea, in a context of vesperal fever, anorexia, and weight loss of 7 kg in two months.

The General examination found a BMI (body mass index) at 18.5 kg/m<sup>2</sup>, a temperature at 37°C, a FR (respiratory rate) at 16 CPM, SpO<sub>2</sub> % at 95% in the open air, with good hemodynamic State.

The pleuropulmonary examination found bronchitis and sibilant rails, while ganglionic areas were free and the remainder of the somatic examination was uncharacteristic.

The biological balance shows a slight inflammatory syndrome with a CRP at 25 mg/l, the quantiferon test (IGRAS: interferon gamma release assay) was positive and HIV serology was negative.

The x-ray of the thorax was without particularity whereas the thoracic and abdominal CT performed without injection of contrast product showed Mediastinal and coelio mesenteric adenopathy (Figure 1).



**Figure 1:** Thoracic CT performed without a contrast product injection showing some intertracheal adenopathy with minimal bilateral pleural effusion (reported cases).

The anatomopathological result of the biopsy of a mesenteric ganglion by coelioscopy is found a granuloma epithelioid and gigante cell with casein necrosis which has to pose the diagnosis of ganglionic tuberculosis. It was decided to put the patient under initial tritherapy excluding ethambutol, by choosing the minimum doses: 15 mg/kg/d of PZA, 5 mg/kg/d of RMP, 4 mg/kg/day of INH, with a take six days out of seven before the hemodialysis session, and supplementation in Vitamin B6 at a dose of 25 mg/kg/day.

The evolution to one month of treatment was marked by a generalized rash with Erythroderma (Figure 2) and fever at 39°C. The biological balance showed hypereosinophilia at 1550/mm<sup>3</sup> with an increase of the ASAT to 110 IU and the ALAT to 126 IU, which was in favor of a DRESS syndrome.



**Figure 2:** Erythematous eruption and squamous Palmar (reported cases).

It was decided to discontinue the therapeutic anti-tuberculosis Protocol, with hospitalization of the patient and administration of an antihistaminic treatment based on hydroxyzine 100 mg/d. the evolution at 15 days of treatment was favorable with regression of the signs and normalization of the biological balance. It was subsequently decided to introduce test doses to identify the drug in question according to the following scheme: RPM at 75 mg on the first day, then 150 and 300 the next two days. The introduction of INH was characterized by a generalized rash at 150 mg, which was in favor of an allergy to INH. On the other hand, the introduction of the PZA was successful.

It was then decided to put the patient according to the Protocol of 9 RZE with a minimum dose of ETB at 7 mg/kg/d. the patient was followed monthly with an ophthalmologic examination. The evolution at nine months of treatment was favourable.

## Discussion

The reported case has two levels of therapeutic difficulty: the first was in relation to the dosage adjustment related to renal failure, and the second was related to the management of the drug toxidermia following the initial Protocol. This was a hypersensitivity reaction to isoniazid, whose identification required the administration of the test doses.

The main presentations of adverse reactions during first-line anti-tuberculosis treatment are: toxidermia, hepatitis, and neurotoxicity. We will describe the practices to be kept in front of these complications.

### Conduct to be held in front of a hypersensitivity reaction to antibacterials

Antituberculous quadruple therapy is frequently the cause of adverse events, especially immunoallergic reactions, which may be minor requiring no management, or sometimes major, involving vital prognosis and requiring proper management. In order of increasing frequency, EMB, RPM, INH and PZA can induce such effects [4,5].

The allergological balance is necessary to confirm the diagnosis: skin tests, biological tests and tests of specific provocations.

In the presence of a severe hypersensitivity reaction, the treatment is stopped until signs disappear, then the drug in question is identified, by introducing the least suspect at low doses and under supervision in a specialized environment (Table 1).

	1 <sup>st</sup> Day	2 - 3 <sup>rd</sup> Day	4 <sup>th</sup> Day
INH	50 mg	150 mg	300 mg
RPM	75 mg	150 mg	300 mg
PZA	250 mg	500 mg	1g
ETB	100 mg	200 mg	400 mg

**Table 1:** Regimen of test doses during reintroduction of treatment antibacillaire in front of a drug-induced toxiderma.

The indication of habituation is necessary in case of allergy to rifampicin and isoniazid [6] (Table 2).

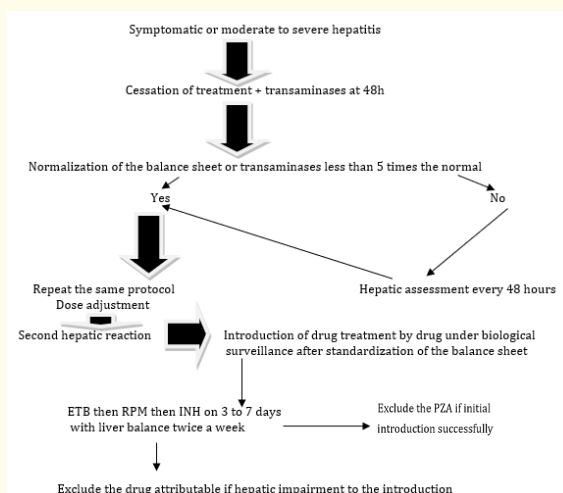
1 <sup>st</sup> Day	t to 0	1/6 cp
	45 min	1/3 cp
	1H 30 min	1/2 cp
	2H 15 min	2/3 cp
	3h	1 cp
	12h	2 cp
	24h	2 cp
2 <sup>nd</sup> Day	36h	5 cp

**Table 2:** Rifater addiction protocol (1 CP of Rifater: 120 mg RPM, 50mg INH and 30 mg PZA).

**Conduct to be held in the presence of hepatotoxicity**

All antituberculosis drugs can cause hepatic reactions with a higher incidence for PZA, estimated at 0.52/100 people months [2,7]. Some associations such as RPM-PZA or PZA-INH potentiate this effect [8]. The hepatic balance allows to classify the severity of the impairment: transaminase values of between three and five times the normal level are mild, five to ten times normal is moderate, and more than ten is severe.

The clinical picture resembles that of viral hepatitis: anorexia, nausea, vomiting, jaundice with the risk of fulminant hepatitis which is all the more feared that the dosages are inadequate, and that a vulnerability is present (alcoholism, disease liver, hepatotoxic treatment). In the presence of a moderate to severe hepatic reaction, the therapeutic Protocol is stopped, with biological monitoring every 48 hours [9]. Figure 3 shows the practical conduct to be followed by hepatotoxicity.



**Figure 3:** Algorithm for supporting hepatic reaction secondary to first-line antituberculosis drugs.

The different alternative protocols in case of toxicity related to an antibacillary or more are illustrated in table 3.

Drug involved	Protocol
Pza	2 RHE/7RH
INH	9 RZE
RPM	3 Km.Lfx.HZE/12Lfx.HZE
PZA and RPM	3 Km.Lfx.HE/12Lfx.HE
PZA and INH	TB.MDR

**Table 3:** Alternative protocols in the case of hepatic toxicity of a first-line antibacillary.

*Km: Kanamycin; LFX: Levofloxacin; TB.MDR: Multidrug-Resistant Tuberculosis.*

### Conduct to respond to neurotoxicity

#### Peripheral neuropathy

The clinical picture is often a distal paresthesia, hypoesthesia with abolition of OSTEO-tendinous and achilles reflexes. It is linked to INH in vulnerable subjects (HIV, bare, renal failure, diabetic) [10]. The dosage of this drug should be reduced in these individuals, with the indication of pyridoxine (active form of vitamin B6) per OS at a dose of 25 mg/d to be taken remotely from INH.

If neuropathy is installed, Pyridoxine is indicated at a dose of 100 to 200 mg without suspending INH.

#### Central attack

Toxic encephalopathy is described with the intake of INH which manifests itself as a fever, metabolic acidosis see reversible convulsion to the injection of pyridoxine.

Psychiatric manifestations ranging from memory disorders to psychotic access can be observed in subjects at risk. Symptomatic treatment is often a rule, see a stop of INH and psychiatric care.

### Conclusion

The international tuberculosis control programme is still part of a multidisciplinary strategic framework, ranging from government commitment to increase human and financial resources, to the proper health care known, with a choice of a correct treatment supplied regularly and continuously.

The improvement of this program is still through a better knowledge of the side effects of treatment as well as their management, sometimes adapting the therapeutic Protocol without compromising the effectiveness of the expected.

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