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Genetic Polymorphisms and Toxicities of First-Line Antituberculosis Drugs: Systematic Review of the Literature

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Abstract

Introduction: Polymorphisms are the main genetic factors associated with toxicities of antituberculosis drugs. This literature review summarizes the polymorphisms of the genes that code for the enzymes of the metabolism of antituberculosis drugs and their transmembrane transporters. Some mechanisms of drug-associated toxicities and strategies for their management have also been described in this review. **Methods:** The bibliographic searches were exclusively carried out in PubMed, over a period of ten years (2010-2020). The search terms were the words "toxicity + antituberculosis drug + one or two word(s) among the following: polymorphism, genetics, mutation, SNP, HLA or haplotype". Publications in English or French, relating to the various toxicities associated with first-line anti-tuberculosis drugs (Rifampicin, Isoniazid, Ethambutol and Pyrazinamide) administered to patients with pulmonary tuberculosis, extrapulmonary tuberculosis or co-infected with TB/HIV were included in this review. Duplicates, in vitro, in silico or drug-induced toxicity studies other than antituberculosis drugs and genetic mutations of Mycobacteria strains were not included. **Results:** The studies selected and included were case reports, cohort studies, original research, systematic reviews and meta-analyses on human subjects of different ethnic origins. Hepatotoxicity is the most common toxicity associated with *NAT2*, *CYP2E1*, *GSTM1* and *GSTT1* polymorphisms in patients on antituberculosis drugs. Other forms of toxicity, less frequent, occurring in certain patients under concomitant treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), antiretrovirals (ARVs), antibiotics or antiepileptics have also been identified. **Conclusion:** The genetic polymorphisms associated with the toxicities of antituberculosis drugs concern both the main enzymes of the metabolic pathways (NAT2, CYP2E1, GST) and the transmembrane transporters (SLCO1B1 and ABCB1). Other genetic

polymorphisms (*TXNRD1*, *SOD2*, *TYMP*) have been suspected but their mechanisms are not yet well understood.

Keywords

Polymorphism, Genetics, SNP, Toxicity, Rifampicin, Isoniazid

1. Introduction

Tuberculosis (TB), a disease caused by Mycobacterium tuberculosis, is the second leading cause of death by infectious disease in adults after HIV/AIDS [1]. According to the current recommendations of the World Health Organization (WHO), the first-line treatment of drug-susceptible TB is a combination chemotherapy of four anti-TB drugs (Rifampicin, Isoniazid, Ethambutol and Pyrazinamide) [1]. Despite its effectiveness, this polychemotherapy has adverse effects that are sometimes serious, mainly occurring during the first trimester of treatment. These side effects can also have a major impact on the outcome of patients' TB treatment [2].

Multidrug therapy for tuberculosis would increase the risk of serious adverse reactions such as hepatotoxicity, gastrointestinal disorders, allergic reactions, arthralgia, neurological disorders and other symptoms [3]. Drug-induced hepatic lesions are the most frequent and most severe encountered during the first trimester of tuberculosis treatment [3]. Among these hepatic lesions, hepatotoxicity could lead to early discontinuation of treatment, thus compromising the effectiveness of tuberculosis control [3]. About 60% of patients on anti-tuberculosis have adverse reactions, one third of which are related to immune sensitization [2]. These cause pressure on health care providers due to their high morbidity, mortality, and increased treatment costs [4].

Depending on the treatment regimen and patient characteristics, the incidence of hepatotoxicity is 2% - 28% [4]. It is manifested by clinical signs (jaundice, gastralgia, nausea, vomiting) associated or not with biological signs (elevation of transaminases > 2 the upper limit of normal values (ULN), elevation of total bilirubin, Gamma-GT and alkaline phosphatase) [5]. Clinical characteristics (HIV status, gender, extrapulmonary tuberculosis), genetic polymorphisms, co-infections with hepatitis B and C viruses as well as certain concomitant treatments constitute high risk factors for liver toxicity during anti-tuberculosis treatment [5] [6] [7].

Isoniazid is the most hepatotoxic major anti-tuberculosis drug but also the most widely used as monotherapy for anti-tuberculosis chemoprophylaxis in non-active tuberculosis patients or in combination with Rifampicin, Pyrazinamide and Ethambutol for the treatment of drug-sensitive tuberculosis. It is mainly responsible for hepatotoxicity associated with polymorphisms of the genes that code for its metabolizing enzymes and/or its transmembrane trans-

porters [5]. These enzymes are N-acetyltransferase 2 (NAT2), cytochrome P450 2E1 (CYP2E1), Glutathione-S-Transferase Mu 1 (GSTM1) and Theta 1 (GSTT1) [4]. The activation capacities of these enzymes are affected by polymorphisms which can alter the chemical composition of antituberculosis drugs and their metabolites in the liver, subsequently causing adverse hepatic effects [4].

Numerous publications have shown that genetic factors constitute one of the main causes of the variability of responses to antituberculosis treatment. According to the first studies conducted in Africa, these genetic factors are very heterogeneous within the populations studied, justifying the need to conduct new studies to identify these genetic factors, determine their frequency and better understand the mechanisms of their involvement in variations in therapeutic responses. This systematic review made it possible to identify the most frequent genetic factors: genetic polymorphisms, haplotypes, genetic associations and gene-environment interactions.

The objective of this review was to summarize the genetic polymorphisms associated with the different toxicities of first-line antituberculosis drugs. Molecular mechanisms of action and strategies for the management of toxicities will also be presented in this review.

2. Methodology

2.1. Bibliographic Research Strategy

The bibliographic search was carried out in PubMed, over a period of ten years (2010-2020). The terms used were the words "toxicity + antituberculosis drug + one or two word(s) among the following: polymorphism, genetics, mutation, SNP, HLA or haplotype".

2.2. Inclusion Criteria

The publications included were in English or French, relating to all the toxicities associated with first-line anti-tuberculosis drugs administered to patients with pulmonary tuberculosis, extra-pulmonary tuberculosis or co-infected with TB/HIV. For publications concerning tuberculosis patients who received in addition to first-line anti-tuberculosis drugs, antiretrovirals or other drugs (antibiotics, non-steroidal anti-inflammatory drugs, antiepileptics, etc.), the inclusion depended on the relevance of the evidence of the imputability of toxicity to anti-tuberculosis treatment. For example, occurrence of toxicity after initiation of anti-TB treatment, favorable outcome after discontinuation of anti-TB treatment or after Pyridoxine supplementation, patients with genetic polymorphisms identified in previous studies and associated with toxicity tuberculosis drugs, etc.

2.3. Exclusion Criteria

The publications excluded were duplicates, studies of toxicity in vitro, in silico or induced by drugs other than antituberculosis drugs, genetic mutations of strains of Mycobacteria (**Figure 1**).

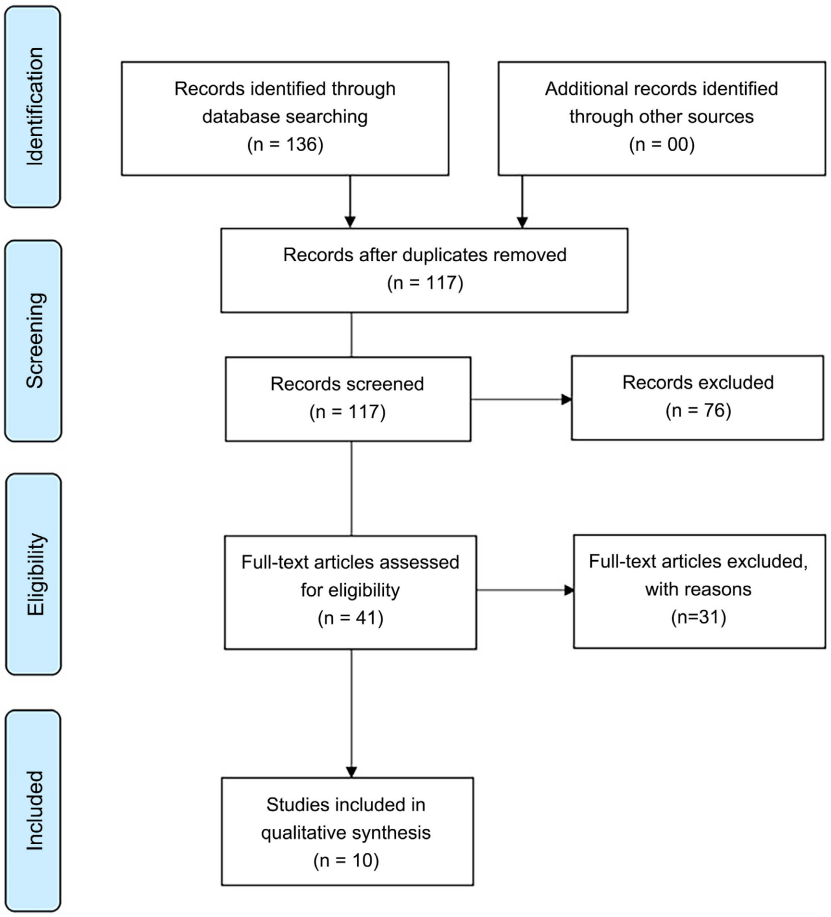

Figure 1. PRISMA flow diagram.

3. Results and Discussion

3.1. Characteristics of Selected Studies

The studies selected were conducted in several countries, included at least one patient (cases reports studies) or several hundred (cases-controls, retrospective, or prospective studies), and the polymorphisms were genotyped by a range of molecular techniques (**Table 1**).

3.2. Toxicities of Anti-Tuberculosis Drugs

Rifampicin, Isoniazid and Pyrazinamide toxicities occur during the intensive phase of anti-tuberculosis treatment [6] [8]. Isoniazid-associated hepatotoxicity is the most frequent and its mechanisms are fairly well known, having been the subject of numerous studies [9]-[13]. Despite its hepatotoxicity, isoniazid is still widely used because it is inexpensive and has potent anti-mycobacterial activity [14].

The toxicities of Rifampicin and Pyrazinamide are unpredictable and their mechanisms less well understood than those of Isoniazid [4]. Finally, toxicities associated with Ethambutol have been rarely described because evidence of its imputability is non-existent or still insufficient [4].

Table 1. Characteristics of selected studies.

Authors	Years	Country	Participants	Treatments	Polymorphisms	Toxicities	Type of study	Genotyping techniques	References
Teixeira *et al.*	2011	Brazil	167	Antituberculosis	*NAT2*, *CYP2E1*, *GSTM1* and *GSTT1*	Hepatitis	Case-control study	PCR-RFLP, multiplex PCR and sequencing	[58]
Kwon *et al.*	2012	South Korea	118	Antituberculosis Antibiotics Antiepileptics NSAIDs[a]	*TTA* haplotype (rs10735393, rs4964287, and rs4595619) of the *TXNRD1* gene	Hepatotoxicity	Retrospective study	Not specified	[50]
Chang *et al.*	2012	Taiwan	98	Antituberculosis	*UGT1A1*	Hepatotoxicity	Prospective study	PCR-RFLP, HPLC on denaturing gel[b], nested PCR and RFLP	[43]
Gupta *et al.*	2013	India	215	Antituberculosis	*NAT2*, *CYP2E1*, *NAT2*4* haplotype	Hepatotoxicity	Prospective cohort study	PCR-RFLP	[32]
Singla *et al.*	2014	India	408	Antituberculosis	*NAT2*, *CYP2E1*, *GSTM1* and *GSTT1*	Hepatotoxicity	Prospective study	PCR-RFLP and multiplex PCR	[19]
Xiang *et al.*	2014	China	2244	Antituberculosis	*NAT2*, *CYP2E1*, *GSTM1* and *GSTT1*	Hepatotoxicity	Cross-sectional study	PCR/Ligase	[3]
Britto *et al.*	2014	Brazil	245	Antituberculosis	*CYP2E1* Rsal, Pstl and *Dral* *GSTM1* and *GSTT1*	Hepatotoxicity	Prospective study	PCR-RFLP and sequencing	[5]
Stettner *et al.*	2015	Germany	01	Isoniazid	*NAT2*, *CYP2E1 c1/c2*	Severe peripheral polyneuropathy	Case report	Not specified	[15]
Guaoua *et al.*	2016	Morocco	205	Antituberculosis	*NAT2*	Hepatotoxicity	Case-control study	PCR and sequencing	[31]
Chamorro *et al.*	2017	Argentina	364	Antituberculosis	*NAT2*, *CYP2E1*, *GSTM1* and *GSTT1*	Hepatotoxicity	Prospective study	PCR, PCR-RFLP and sequencing	[29]
Petros *et al.*	2017	Ethiopia	495	Antituberculosis Antiretrovirals	*HLA-B*	Cholestatic hepatotoxicity	Case-control study	HLA genotyping	[48]
Zara *et al.*	2020	Saudi Arabia	96	Antituberculosis	*NAT2*	Not investigated	Prospective study	PCR and sequencing	[25]

[a] Non-steroidal anti-inflammatories, [b] Denaturing High Performance Liquid Chromatography (DHPLC).

3.3. Genetic Polymorphisms of Metabolizing Enzymes

3.3.1. CYP2E1 Polymorphisms (Cytochrome P450 2E1)

CYP2E1 is an enzyme involved in phase I of isoniazid metabolism [5]. This enzyme leads to the formation of metabolites among which, the more reactive hydrazine, potentiates the direct toxicity of isoniazid.

CYP2E1 polymorphisms have been associated with hepatotoxicities including isoniazid (INH)-induced hepatitis [5]. The *c1/c2* genotype of *CYP2E1* polymorphisms (*CYP2E1 c1/c2*) and those of *NAT2* were also associated with the development of severe polyneuropathy (PNP) in a 23-year-old man who received INH-containing therapy [15]. Indeed, during his treatment, laboratory results had shown incipient liver and kidney damage [15]. Later, the genetic analyzes carried out revealed the existence of these two polymorphisms in the patient [15].

CYP2E1 has been associated with isoniazid-induced hepatotoxicity due to its

ability to activate acetylhydrazine, subsequently forming various hepatotoxins [16]. There is evidence associating CYP2E1 levels with interindividual variation [16]. The *CYP2E1*5* allelic variant is common in Japanese (Frequency 0.27) but rare in Europeans (Frequency 0.02). Isoniazid's toxic metabolites can also cause other toxicities such as peripheral neuropathy and maculopapular rash [4].

Isoniazid hepatotoxicity was significantly associated with the *CYP2E1 RsaI* polymorphism and the 96 bp deletion-insertion single nucleotide polymorphism of the *CYP2E1* gene [1]. Patients with a homozygous or heterozygous mutant genotype for the *CYP2E1 RsaI* polymorphism are less likely to present with hepatotoxicity compared to homozygous wild-type patients [1]. On the other hand, the *CYP2E1 DraI* and *PstI* polymorphisms are not significantly associated with isoniazid-induced hepatotoxicity [1].

In the absence of discontinuation of antituberculosis treatment, hepatotoxicity can lead to death in 6% to 12% of cases [1].

According to Wang et al., the *CYP2E1* c1/c1 genotype significantly increases the risk of isoniazid-induced hepatotoxicity [1]. Isoniazid reactive metabolites destroy hepatocytes by directly interfering with cellular homeostasis or by triggering immunological reactions [17].

The hepatic enzyme CYP2E1 is thought to be involved in the metabolism of Rifampicin [18]. Indeed, its polymorphisms have been associated with elevated plasma concentrations of Rifampicin in poor CYP2E1 metabolizers [18]. Some TB patients who were extensive metabolisers had higher hepatic cytolysis (ALT, AST) and biliary stasis (Gamma-GT) indices compared to poor metabolisers before and after hospital treatment [18].

CYP2E1 polymorphism is a genetic marker of susceptibility to hepatotoxicity before and during antituberculosis treatment [18]. However, Xiang et al. found no association between hepatotoxicity and *CYP2E1 RsaIc1/c1*, *CYP2E1 RsaIc1/c2*, or *c2/c2* polymorphisms [3].

The pathogenetic mechanism of antituberculosis drug-induced hepatotoxicity is still unclear. A better understanding of this mechanism would help guide the medical approach for rapid and optimal patient care. The combination of Isoniazid and Pyrazinamide would increase the risks of hepatotoxicity from Isoniazid. It is therefore possible that there is a drug interaction potentiating the hepatotoxicity of isoniazid.

Hepatotoxins (Hydrazine or acetylhydrazine) generated by CYP2E1 or NAT2 are detoxified after conjugation by Glutathione S-Transferases (*GSTM1* and *GSTT1*) in the liver [3]. Acetylhydrazine can also be detoxified after a second acetylation by NAT2 forming diacetylhydrazine, a non-toxic metabolite of isoniazid. Antituberculosis metabolizing enzymes are polymorphic and their distribution varies according to ethnic groups [3].

The heterozygous *CYP2E1 c1/c2* genotype would contribute to a high risk of hepatotoxicity [19]. On the other hand, the absence of the "c2" allele in women would be a protective factor against the onset of hepatotoxicity, while in men,

the presence of the "*c1/c2*" allele would contribute to a high risk of onset. hepatotoxicity [19].

In *CYP2E1*, two polymorphisms are most commonly studied (RsaI/*PstI* (rs-2031920/rs3813867) and *DraI* (rs6413432). A recent meta-analysis revealed that the RsaI/*PstI* c1/c1 polymorphism confers a higher risk of hepatotoxicity induced by Isoniazid compared to *c1/c2* or *c2/c2* genotypes, but no increased risk of *DraI* polymorphism [20]. Isoniazid may also cause peripheral neuropathy in some patients during treatment [21].

CYP2E1 could be a good genetic marker of isoniazid -induced hepatotoxicity but larger studies are needed to validate its relevance as a risk factor [16].

3.3.2. Polymorphisms of NAT2 (N-Acetyltransferase Type 2)

NAT2 is one of the phase II enzymes that plays an essential role in the detoxification and metabolism of several environmental toxins and many drugs including Isoniazid [17] [22] [23]. It is the main cause of toxicity of antituberculous drugs in patients carrying mutations [24]. It is mainly found in the liver and intestine [25].

The NAT2 enzyme is encoded by the highly polymorphic *NAT2* gene with 108 haplotypes in the general population [26]. *NAT2* polymorphisms are responsible for a tri-modal distribution of isoniazid pharmacokinetics [27]. Thus, a distinction is made between slow, intermediate or normal and fast acetylators [27]. Slow acetylators are at risk of hepatotoxicity while fast acetylators face treatment failure [27]. The seven most common *NAT2* polymorphisms are located at its exon 2 [26].

About 35 different *NAT2* alleles have been reported in the Indian population [28]. The *NAT2*4* allele has historically been referred to as "wild type" because it is most common in certain ethnic groups [28]. The *NAT2* polymorphisms allowed to distinguish 3 phenotypes of acetylators: the fast acetylators (Homozygotes having two fast alleles), the intermediate acetylators (Heterozygote having a fast allele and a slow allele) and the slow acetylators (Homozygotes, having two slow alleles) [28]. Of these three acetylator phenotypes, the slow acetylator phenotype is clinically the most important [28]. On the other hand, in TB/HIV co-infected patients, there would be a discrepancy between the genotype and the *NAT2* acetylator phenotype [28].

The combination of the slow acetylator profile and the c2 variant of the *CYP2E1* gene is responsible for an increase in the hepatotoxicity of antituberculosis drugs [29]. A case of isoniazid-induced polyneuropathy has been reported in a 23-year-old patient, carrier of *NAT2* and *CYP2E1* mutations [15].

Renal failure is also a risk factor for isoniazid-induced hepatotoxicity [14]. In addition, other toxicities linked to the existence of a co-morbidity can also occur during the antituberculous treatment associating isoniazid. Thus, a severe case of encephalopathy was reported in a 71-year-old patient of African origin after being put on anti-tuberculosis treatment [14].

In hemodialysis patients and carriers of the slow isoniazid acetylator pheno-

type, a reduction in the dosage of isoniazid associated with an increase in the doses supplemented with Vitamin B6 or Pyridoxine (>100 mg/day instead of 10 - 25 mg/day) reduce the occurrence of hepatotoxicity, encephalopathy and neuropathy [14].

Isoniazid hepatotoxicity occurs by a molecular mechanism that depends on the presence of active alleles of the *NAT2* gene (*NAT2*4* and *NAT2**12) [14].

In a study conducted in 2020 by Zahra et al., four new haplotypes *NAT2*5TB*, *NAT2*5AB*, *NAT2*5ZA* and *NAT2*6W* corresponding to the slow acetylator phenotype were identified [25]. The most frequent single nucleotide polymorphisms and haplotypes in the participants of this study were *NAT2* 803 A > G (0.510) and *NAT2* 341T > C (0.427), respectively, then *NAT2*6C* (25.00%) and *NAT2*5A* (22. 92%) corresponding to the slow acetylator phenotype [25].

The effectiveness of isoniazid-based chemotherapy depends on the acetylator status or phenotype and the patient's medical condition [27]. Yet, a standard FDA-recommended dose is administered regardless of acetylator phenotype or immune status resulting in adverse effects occurring in 5% - 33% of patients [27]. Specific dose adjustments according to acetylator phenotype have been suggested to ensure optimal treatment results [27]. Thus, a reduced dose administered to slow acetylators significantly reduces exposure to toxic metabolites and therefore the risk of adverse events, while maintaining sufficient treatment efficacy [27]. In contrast, intermediate and rapid acetylators receive higher doses of isoniazid on a twice-daily schedule [27].

Slow acetylator phenotype, *CYP2E1 c2* or *A4* variant genotype, and female gender are significantly associated with anti-TB drug-induced hepatotoxicity in some TB patients [29]. Patients with the slow acetylator profile and the c2 variant are more at risk of developing hepatotoxicity [29]. In some patients carrying the *GSTT1* and *CYP2E1* polymorphisms, there is a synergistic interaction leading to epistaxis and increasing the risk of hepatotoxicity [29].

The increase in plasma concentrations of isoniazid following accumulation by slow acetylators exposes them to toxic effects, in particular hepatotoxicity [4]. It may also benefit the therapeutic efficacy of isoniazid [4]. On the other hand, in fast acetylators, the plasma concentrations of isoniazid are lower with the consequences of the absence of toxicity, the reduction of the efficacy of the drug, therapeutic failure and the appearance of resistant strains of mycobacteria [4]. Fast acetylators are homozygotes of the *NAT2*4*, *NAT2*11A*, *NAT2*12A*, *NAT2*12B*, *NAT2*12C* or *NAT2*13* alleles. On the other hand, heterozygous subjects or carriers of the wild-type allele are respectively intermediate or slow acetylators [4].

Isoniazid has been associated with a case of severe encephalopathy in a chronic hemodialysis patient [14]. Investigations revealed that he had a slow acetylator phenotype and that Pyridoxal phosphate, the active metabolite of Pyridoxine used for supplementation, would have been removed by dialysis [14]. The risk of isoniazid toxicity is high in hemodialysis patients with *NAT2* polymorphisms

[14].

The incidence of hepatotoxicity induced by antituberculosis drugs including isoniazid ranges from 1% to 36%, and mortality in such cases is not uncommon [30]. *NAT2* exhibits a hereditarily determined polymorphism [30].

There are approximately 36 *NAT2* polymorphisms reported in the literature [17]. Fast acetylators metabolize INH five to six times faster than slow acetylators [17].

The slow C 481 A 590 G 857 haplotype and an intermediate acetylator T 481 A 590 G 857 haplotype have been associated with the development of hepatotoxicity [19].

NAT2 genotypes (*NAT2*5/*5*, *NAT2*5/*6*, *NAT2*6/*6* and *NAT2*6/*14*) corresponding to the slow acetylator profile are very frequent in certain countries such as Morocco (78%) [31].

The major *NAT2*4* haplotype would protect against hepatotoxicity [32]. The increased susceptibility to Isoniazid (INH)-induced hepatotoxicity due to the presence of *NAT2* polymorphism has been demonstrated in the West Indian population [32].

The prevalence of isoniazid-induced hepatotoxicity was higher in men than in women, and there was a weak association with *NAT2*5* genotypes [3]. In Uyghur tuberculosis patients in Xinjiang, China, liver damage has been associated with the *NAT2*5* genetic variant [3].

Multidrug therapy for tuberculosis increases the risk of serious adverse drug reactions such as hepatotoxicity, gastrointestinal disorders, allergic reactions, arthralgias, neurological disorders and other symptoms [3]. Hepatotoxicity results from the production of toxic metabolites associated with the presence of hepatic enzyme polymorphisms [3].

Several candidate single nucleotide polymorphisms have been identified but their clinical utility in predicting isoniazid-induced hepatotoxicity remains uncertain [20]. The *NAT2* polymorphisms rs1041983 and rs1495741 have been associated with isoniazid hepatotoxicity in a Singaporean population and have demonstrated clinical utility in the prediction of INH-induced hepatotoxicity [20].

Isoniazid can cause asymptomatic elevation of liver enzymes in 10% - 20% of patients on treatment, clinically significant hepatitis, or even in less than 1% of cases, acute liver failure [21]. Risk factors associated with Isoniazid hepatotoxicity are age, female gender, black race, alcoholism, liver disease, and concurrent use of other drugs such as Rifampin and Pyrazinamide [21]. The molecular mechanisms of isoniazid hepatotoxicity are not yet well understood, but the accumulation of toxic intermediate metabolites is thought to play an important role [21]. From another point of view, pharmacogenetic studies have so far only focused on the main enzymes (NAT2, CYP2E1 and GST) directly involved in the metabolism of isoniazid [21].

Isoniazid hepatotoxicity usually occurs between 2 weeks and 6 months after

the start of treatment. The late onset of isoniazid hepatotoxicity indicates the existence of an immunological mechanism that may involve the antioxidant and detoxification pathway genes, the human leukocyte antigen (HLA) system and tumor necrosis factor-α (TNF-α) [21].

Of the many *NAT2* polymorphisms, seven alleles (rs1801279, rs1041983, rs1801280, rs1799929, rs1799930, rs1208, and rs1799931) define 34 haplotypes, but most studies consider only a subset to determine the acetylator phenotype of patients [21]. A novel *NAT2* polymorphism rs1495741 has recently been associated with isoniazid hepatotoxicity, although it may not be a good marker for determining the acetylator phenotype of patients [21].

Reactive metabolites of isoniazid may cause peripheral neuropathy or maculopapular eruptions [4].

NAT2 polymorphisms have also been associated in some studies with bladder cancer, colorectal cancer, rheumatoid arthritis, and diabetes mellitus [25].

In addition to genetic polymorphisms, environmental factors and concomitant drug intake can modulate the activity of antituberculosis metabolizing enzymes [28]. Thus it has been reported that Isoniazid would cause the decrease in the clearance of many drugs such as Phenytoin, Carbamazepine, Diazepam, Vincristine, and Acetaminophen. [28]. For example, in patients with tuberculous meningitis or tuberculoma having convulsions, the simultaneous use of Isoniazid and Phenytoin leads to an increase in plasma concentrations of the latter and the appearance of its intoxication [28].

It is important to determine the phenotypic status of patients before starting them on an antituberculous treatment regimen including isoniazid [26]. *NAT2* genotyping could serve as a marker for the identification of patients predisposed to hepatotoxicity of antituberculosis drugs [32].

3.3.3. Polymorphisms of GSTs (Glutathione S-Transferases)

GSTs represent a superfamily of enzymes involved in phase II reactions in the metabolism of many drugs, including antituberculosis drugs [33]. They play a protective role in the processes of biological detoxification of drugs by catalysing the conjugation reactions of Glutathione and toxic intermediate metabolites, subsequently facilitating their elimination and then reducing their hepatotoxicity [33]. They exist in two forms (oxidized and reduced) and are involved in maintaining the redox potential of the cytoplasm of hepatic cells [34].

GSTs hydrolyze acetylhydrazine, the hepatotoxic metabolite of isoniazid [29]. These enzymes detoxify a variety of drugs by conjugation with glutathione. They also play a role in the detoxification of the products of oxidative stress [16].

The *GSTM1* and *GSTT1* isoforms are absent in several individuals because of the large genetic deletions resulting in null genotypes. Carriers of these null genotypes have no functional enzymatic activity and do not express the proteins [34]. It is possible that the *GSTM1* and *GSTT1* genotypes influence the risk of isoniazid-induced hepatotoxicity. Several independent studies have found an association between *GSTM1 null* genotypes and hepatotoxicity [35] [36]. The re-

sults of these studies had demonstrated that the frequencies of *GSTM1 null* genotypes were higher among the cases of hepatotoxicity in contrast to the controls [35] [36].

GST deficiency is due to mutations in the Glutathione S-Transferase Mu 1 (*GSTM1*) and Glutathione S-Transferase Theta 1 (*GSTT1*) *null* genes [29]. The genetic polymorphisms frequently associated with the toxicity of antituberculosis drugs are those of the genes Glutathione S-Transferase Mu 1 (*GSTM1*), Glutathione S-Transferase Theta 1 (*GSTT1*), and Glutathione S-Transferase Pi 1 (*GSTP1*) [5] [35] [37] [38]. However, deletions of the *GSTM1* and *GSTT1* genes are not associated with drug toxicity [39]. The high frequencies of deletions of the *GSTM1* and *GSTT1* genes in human populations would explain the interindividual variability of the metabolism of xenobiotics [5].

Null genotypes of the *GSTM1* and *GSTT1* genes are risk factors for hepatocellular carcinoma [40]. Indeed, these genes would be involved in the mechanisms of detoxification of environmental carcinogens, environmental toxins and radicals resulting from oxidative stress [40]. *GST* genes in the occurrence of hepatotoxicity and schizophrenia in patients on antituberculosis drugs has been reported [41]. In the Iranian population, the distributions of genetic polymorphisms of *GSTT1* are more significant than those of other *GSTs* [42]. *GSTM1* and *GSTT1* gene deletions (42.9% and 12.4% respectively) in Brazilian populations, these are not associated with the toxicity of antituberculosis drugs [5]. However, this mutation has no influence on drug response [5].

There is a synergistic interaction between the *GSTT1* and *CYP2E1* genes associated with an increased risk of anti-TB drug-induced hepatotoxicity [29]. Isoniazid inhibits *CYP2E1* activity less in individuals carrying the *CYP2E1* *1A/*1A genotype compared to other genotypes [4]. Therefore, people carrying the *CYP2E1* *1A/*1A genotype would have higher *CYP2E1* activity, which leads to the formation of a greater amount of hepatotoxins [4]. Rifampicin and Pyrazinamide have also been associated with hepatotoxicity of antituberculosis drugs [4]. However, their mechanisms are still unknown and unpredictable. *OATP1B1* transmembrane transporter polymorphisms have been associated with rifampicin toxicity [4]. Several studies have shown that if *GST* is not expressed, there will be an accumulation of reactive metabolites, which increases their interactions with cellular macromolecules [17].

East Asian patients carrying a *GSTM1 null* genotype have a higher risk than Caucasians, while Caucasians carrying a homozygous *GSTT1* null genotype are at higher risk of hepatotoxicity unlike Asian patients. *GST* polymorphisms are highly variable depending on the ethnic groups and the age of the patients [33]. The association between *GSTM1*/*GSTT1* null mutations and an increased risk of anti-TB drug hepatotoxicity has been demonstrated in adults. On the other hand, in children, there would be no significant association.

3.3.4. Polymorphisms of UGTs (UDP-Glucuronosyl-Transferases)

UDP-Glucuronosyl-Transferases (UGT) are phase II enzymes in the metabolism

of certain drugs, including isoniazid. They are responsible for the glucuronidation of endobiotics and xenobiotics [43]. These enzymes are often considered detoxifiers although they also have roles in the formation of reactive intermediates such as acylglucuronides, responsible for hepatotoxicities [16].

UGT1A1 polymorphisms lead to detoxification deficit of free bilirubin and organic anions such as Rifampicin [43]. These genetic mutations are responsible for a double toxicity on the one hand due to the accumulation of free bilirubin and on the other hand, by default of elimination of the metabolites of Rifampicin. The heterozygous variants *UGT1A1*27* and *UGT1A1*28* would be associated with a high risk of hepatotoxicity in Taiwanese patients [43].

Rifampicin can induce cytochrome P450 3A4 and increase the formation of a by-product, 6-Alpha-hydroxylated bile acid requiring UGT for glucuronidation before renal excretion [43].

Subject to confirmation of this association by studies on a larger number of patients, screening for *UGT1A1* polymorphisms before treatment for tuberculosis may reduce the incidence of ATDH and improve compliance with treatment [43].

3.4. Polymorphisms of Transmembrane Transporters

Transporters are membrane proteins whose main function is to facilitate the flow of molecules into or out of cells [44]. They are also involved in the bioavailability, therapeutic efficacy and pharmacokinetics of various drugs [44]. There are many genetic polymorphisms of the two main families of ABC and SLC transporters.

Polymorphisms and haplotypes of the genes coding for these transporters do not lead to drug-induced hepatitis in Korean patients on antituberculous drugs [45].

3.4.1. P-Glycoprotein Polymorphisms

P-glycoprotein is a transmembrane efflux pump whose synthesis is encoded by the ABCB1 gene, the polymorphisms of which are responsible for resistance to drugs transported by this protein [46]. Among these drugs, resistance to Rifampicin and Ethambutol has not yet been fully elucidated [46]. However, findings from some studies associate ABCB1 polymorphisms and other risk factors with Ethambutol resistance [46]. It should be noted that these resistances are not always of bacterial origin but sometimes linked to the host [46].

3.4.2. MRP2 Polymorphisms

MRP2 or multi-drug resistance protein 2 is a transmembrane protein whose synthesis is encoded by the ABCC2 gene. This protein transports bilirubin out of liver cells and into bile.

More than 40 ABCC2 polymorphisms have been associated with Dubin-Johnson syndrome. It is a disease characterized by yellowing of the skin and the whites of the eyes, which usually appears in adolescence or early adulthood. The major-

ity of mutations are single nucleotide polymorphisms that alter a single amino acid in the primary sequence of the MRP2 protein.

3.4.3. OATP1B1 Polymorphisms

The *SLCO1B1* gene (Solute Carrier Organic Anion transporter family member 1B1) codes for the synthesis of a transmembrane protein, the organic anion transporter polypeptide 1B1 (OATP1B1). This protein present in the hepatocyte ensures the transport of endogenous substances (bilirubin, hormones, various toxins, etc.) and xenobiotics (statins, antihypertensives, anticancer drugs, antibiotics, etc.) from the blood to the liver for their elimination. *SLCO1B1* polymorphisms have been associated with impaired transport functions of the OATP1B1 protein. This is because the mutated protein produced is less efficient in transporting compounds through the liver, leading to elevated levels of compounds in the body. Certain *SLCO1B1* polymorphisms are implicated in Rotor syndrome manifesting as elevated levels of bilirubin in the blood. In some cases, the disease is caused by a deletion that removes parts of the *SLCO1B1* gene so that no functional OATP1B1 protein is produced. Genetic polymorphisms of this transporter are associated with rifampicin toxicity [4]. However, the scientific evidence for this association is still insufficient.

3.5. HLA Polymorphisms

They are mainly responsible for the occurrence of allergic reactions and other undesirable effects during anti-tuberculosis treatment. Many HLA alleles have been associated with hepatotoxicity of antituberculosis drugs in tuberculosis patients or patients co-infected with TB/HIV [47]. For example, the HLA-DBQ1*0201 allele is associated with hepatotoxicity of antituberculosis drugs in some Indian patients [16].

The strongest associations were observed with HLA class I and II genes. The mechanism underlying the association of HLA polymorphisms with antituberculosis drug toxicity could involve T cell responses to drug-protein adducts or drug alone, but requires further investigation.

Antituberculosis drug toxicity reactions can be classified into immune-mediated toxicity and non-immune-mediated toxicity [16]. In humans, these two toxicities are encoded by the Major Histocompatibility Complex located on chromosome 6, in a highly polymorphic region of the genome [16]. Immune-mediated liver toxicity reactions may involve the formation of a covalent complex between the drug or its metabolite and cellular proteins. This complex will then be presented to T cells by the particular HLA molecules resulting in an inappropriate local response that can subsequently cause cellular damage [16]. Drugs can also interact directly with HLA molecules and induce a T cell response without initial formation of a covalent complex.

In general, HLA associations are an important component of genetic susceptibility to drug-induced hepatotoxicity. However, it is possible, as in the hepatotoxicity of isoniazid, that the association is weakly significant, as is the case in

Indian patients carrying the HLA-DQB1*0201 allele [16]. It is therefore possible that some additional factors or other genes add to the HLA to contribute to the genetic susceptibility to anti-TB drug hepatotoxicity.

Some TB/HIV co-infected patients carrying the *HLA-B**57 alleles (B*57:03 and B*57:02) are likely to develop cholestatic-type hepatotoxicity induced by antituberculosis drugs and ARVs [48].

Antituberculosis drugs can also be responsible for severe adverse cutaneous effects, the prevention and confirmation of which are difficult [49]. *HLA-B* alleles have been associated with the occurrence of these adverse effects [49].

HLA-B pre-screening can only identify a small minority of subjects at risk of developing severe cutaneous adverse effects. On the other hand, the cells releasing the specific IFN-γ of the antituberculosis drug are detectable in approximately half of the patients. Identifying the anti-tuberculosis drug responsible for the side effects requires the search for new strategies for better prevention [49].

Some severe adverse skin reactions are life-threatening. These include acute generalized pustular exanthematous reactions, drug reactions with eosinophilia and systemic symptoms, Stevens-Johnson syndrome (SJS) and toxic epidermal necrosis (TEN) [49].

Several studies have shown that *HLA-B* alleles are strongly associated with an elevated risk of drug-induced adverse skin effects [49]. *HLA-B* screening genotyping may be beneficial in preventing these *HLA-B* allele cutaneous adverse effects. However, it should be noted that systematic *HLA-B* pre-screening before the prescription of certain drugs in high-risk populations has not yet been approved by a working group of experts.

The tools currently available for the identification and confirmation of the suspected drug, the skin test and the lymphocyte transformation test (LTT), are only recommended for patients after remission from a drug allergy episode [49]. Use of the enzyme immunoassay ELISpot can be considered as is the case in patients who have presented with a maculopapular exanthema or an anaphylactic reaction due to the use of certain anti-infectives (Amoxicillin, Cephalosporins, etc.) [49]. Indeed, this test, which can be performed during the acute stage of drug allergy, has shown a higher sensitivity than LTT and a positive response even in patients who were taking immunosuppressive drugs [49].

3.6. Haplotypes

A haplotype of *NAT2* polymorphisms was identified in a 71-year-old patient, on hemodialysis, of African origin, in whom severe encephalopathy occurred after taking isoniazid [14]. This is the only case reported in one of the articles in this literature review. It is quite possible that other cases have not been published or that they have been reported in a journal not indexed in the PubMed bibliographic database that we used exclusively for this study.

Rifampicin liver toxicity has been associated with the *OATP1B1*15* haplotype identified as an important risk factor [1].

3.7. Other Genetic Polymorphisms

Some genetic polymorphisms initially identified in animals have been found in some patients with hepatotoxicity induced by antituberculosis drugs. This is the example of the thioredoxin reductase 1 (*TXNRD1*) gene identified as a candidate marker of hepatotoxicity [50].

The *SOD2* polymorphism (gene encoding the mitochondrial protein MnSOD) is a predictive factor for hepatotoxicity of antituberculous drugs and other therapeutic classes [51]. Indeed, the MnSOD protein generates toxic hydrogen peroxide for liver cells. This polymorphism, also associated with higher MnSOD activity, is a risk factor for cellular and/or cholestatic damage [51]. In cases of hepatic cholestasis, *GPX1* polymorphisms are more common with reduced activity levels [51]. In some patients, there are strong associations of *SOD2*/*GPX1* polymorphisms [51].

Polymorphisms in genes encoding inflammatory mediators may contribute to the susceptibility to hepatotoxicity of many drugs, including antituberculosis drugs [51].

Ethambutol has been associated with toxic optic neuropathies that occur in patients with mutations in a fusion gene, *OPA1*, responsible for the autosomal dominant inheritance of optic atrophy [52]. A case of *CMT2A2* (*MFN2* Mutation: T669G, F223L) has been reported in a patient who received Ethambutol and subsequently developed accelerated weakness, vocal cord paralysis and optic atrophy [52]. The deterioration in the patient's condition began one month after the start of treatment and stabilized on discontinuation of treatment followed by improvement in visual fields [52]. This case shows that patients with *CMT2A2*, and possibly other mitochondrial fusion defects, may be particularly susceptible to ethambutol-induced neurotoxicity [52].

Mutations in the *TYMP* gene have also been associated with a case of mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), a rare autosomal recessive multisystem disease [53]. A first case of an MNGIE patient diagnosed in Bulgaria carrying a new homozygous *TYMP* mutation (p.Leu347Pro) has been reported [53]. This patient had presented several months after the start of anti-tuberculosis treatment, gastrointestinal disorders, cachexia, hearing loss, ptosis, ophthalmoparesis, polyneuropathy, cognitive disorders and leukoencephalopathy of the brain [53]. His motor ability had drastically diminished, making him dependent on a wheelchair [53]. This case suggests the existence of mitochondrial toxicity of antituberculosis drugs in some patients carrying *TYMP* mutations [53].

Drug-induced hepatotoxicity due to some anti-infectives is related to polymorphisms in the human leukocyte antigen (HLA) region [54]. Thus the HLA-DQB1*06:02 polymorphism has been associated with the hepatotoxicity of Amoxicillin-Clavulanic Acid, *HLA-B**57:01 with that of Fucloxacillin, etc. [54]. GWAS results offer molecular insights into the central role of the immune system in idiosyncratic drug-induced hepatotoxicity [54]. It is therefore not ex-

cluded that certain HLA polymorphisms are also associated with the various forms of toxicity of antituberculosis drugs.

3.8. Associations of Genetic Polymorphisms

It is not uncommon to encounter in some patients, an association of *CYP2E1*, *NAT2*, *GST*, and *SLCO1B1* polymorphisms [55]. In these patients, the manifestations of the toxicity of antituberculosis drugs are severe and can lead to death.

Hepatotoxicity is only observed in patients carrying combination polymorphisms including the *NAT2* gene [5]. There is no synergistic effect between *CYP2E1*, *GSTM1*, and *GSTT1* polymorphisms [5]. On the other hand, there is a very significant association between hepatotoxicity, slow phenotype of the *NAT2* gene and polymorphism of the *CYP2E1* gene.

Isoniazid was associated with severe PNP in a 23-year-old man, with liver and kidney damage [15]. Genetic analyzes revealed the presence of a combination of *NAT2* and *CYP2E1 c1/c2* polymorphisms in this subject [15]. These two polymorphisms having been associated with a high risk of toxicity would justify the neurological, hepatic and renal toxicities reported in this subject [15]. Individual genotyping, performed before treatment or at least if elevated liver parameters are observed, can reduce the risk of severe cases of PNP by early adjustment of treatment [15].

3.9. Interactions between Genes, Environmental Factors and Toxicity of Antituberculosis Drugs

Several genes associated with the toxicity of antituberculosis drugs may be present in some patients, thus increasing the toxic effects. This is the example of the *CYP2E1* and *GSTT1* genes which interact by increasing the hepatotoxicity of antituberculosis drugs [29]. Adverse effects of anti-tuberculosis drugs are also linked to the interaction between the *NAT2*, *GSTM1*, *GSTT1*, *CYP2E1* genes and environmental factors [56]. There is no association between liver toxicity and *GSTM-1*/*GSTT1* gene interaction [57].

There are synergistic interactions between *GSTT1* and *CYP2E1* polymorphisms manifested by epistaxis associated with an increased risk of hepatotoxicity. A significant gene-environment interaction is also associated with an increased risk of hepatotoxicity [29].

Slow acetylator profile, *CYP2E1* c2 or *A4* variant genotype, and female sex are significantly associated with antituberculosis drug-induced hepatotoxicity [29]. Patients carrying the slow acetylator profile and the c2 variant are more at risk of developing hepatotoxicity [29]. In some patients with *GSTT1* and *CYP2E1* polymorphisms, there is a synergistic interaction leading to epistaxis and increasing the risk of hepatotoxicity [29].

3.10. Management of Adverse Effects

The etiology of severe skin reactions occurring in some patients on anti-tuberculosis treatment can be determined by the patch test [2]. However, systemic

reactions to this test are particularly common in TB/HIV co-infected patients [2]. In vitro tests are still limited to specialized centers, but specific lymphocyte responses to antituberculosis drugs have been identified in patients with skin and/or liver reactions.

Desensitization of patients with severe skin reactions is possible but very risky [2]. The management of these patients remains sub-optimal [2].

Patients with chronic renal failure on hemodialysis with a slow acetylator phenotype are at risk of developing encephalopathy [14]. One of the hypotheses that could explain the occurrence of this encephalopathy would be the elimination of pyridoxine phosphate (active metabolite of pyridoxine) by dialysis and the accumulation of isoniazid and/or its toxic metabolites in the blood of patients [14]. Discontinuation of isoniazid with supplementation with high doses of pyridoxine resulted in a favorable outcome [14]. Caregivers should be aware of the risk of isoniazid toxicity that may occur in hemodialysis patients receiving isoniazid or a tuberculosis treatment regimen containing this isoniazid [14]. Context-appropriate prescribing of either high doses of Pyridoxine or reduced doses of Isoniazid can reduce the risk of life-threatening Isoniazid toxicity in patients on hemodialysis and/or slow acetylators [14].

4. Conclusion

Hepatotoxicity is the most frequent of first-line antituberculosis drugs toxicities. The genetic polymorphisms associated with their toxicities concern the metabolizing enzymes (NAT2, CYP2E1, GST) and membrane transporters (SLCO1B1 and ABCB1). Other genetic polymorphisms have been suspected but their effects depend in some cases on interactions between genes or genes-environment. Genetic polymorphisms could be used to screen high-risk patients and guide the choice of a more effective and safe treatment.

Contribution of the Authors

SS (Bibliographic research, drafting of the manuscript). All authors have read, commented on and approved the final manuscript.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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