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GSTT1 and *GSTM1* null mutations and adverse reactions induced by antituberculosis drugs in Koreans

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SUMMARY

Adverse reactions induced by antituberculosis drugs (ATD) often result in serious morbidities, impeding scheduled treatment and cure. In the development of ATD-induced adverse reactions, glutathione *S*-transferase has been suggested to play a protective role as an intracellular scavenger by conjugating toxic reactive metabolites of ATD. This study examined the association of null mutations in GST enzyme genes (*GSTT1* and *GSTM1*) with the development of ATD-induced hepatitis and cutaneous reactions. We compared the frequencies of *GSTT1* and *GSTM1* null mutations in 57 patients with hepatitis, 94 patients with cutaneous adverse reactions, and 190 ATD-tolerant controls. The frequency of null mutations in *GSTT1* and *GSTM1* in patients with ATD-induced hepatitis was not significantly different from that of controls (59.6% vs. 54.2% and 45.6% vs. 54.7%, respectively). Additionally, no significant difference was observed in the frequency of either null mutation in patients with ATD-induced cutaneous reactions, including maculopapular eruption, compared with controls (58.5% vs. 54.1% for *GSTT1* and 59.6% vs. 54.6% for *GSTM1*). These findings indicate that *GSTT1* and *GSTM1* null mutations are not associated with the development of ATD-induced hepatitis or cutaneous reactions in this Korean population, and suggest that glutathione *S*-transferase enzymes do not play important roles in the pathogenesis of these conditions.

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1. Introduction

Tuberculosis (TB) remains a serious infectious disease, causing significant morbidity and mortality. Guidelines for TB management recommend a combination regimen including isoniazid (INH), rifampin, ethambutol, and pyrazinamide as the first-line treatment.[1] This regimen often causes adverse drug reactions, such as hepatitis, cutaneous reactions, gastrointestinal upset, and drug fever.[2] Although mild reactions can be tolerated or managed with symptomatic therapy, serious cases require discontinuation of medication and prolongation of the treatment period.

Although some demographic and clinical factors have been reported to increase the risk of hepatitis induced by anti-TB drugs (ATD),[3,4] mechanisms for ATD-induced adverse reactions are not well understood. One prevailing theory for adverse drug reactions is the hapten hypothesis.[5] Drugs are not immunogenic in most cases; however, reactive metabolites generated by drug metabolism can bind to a high-molecular-weight protein and initiate an immune response. In this process of bioactivation, drug-metabolizing enzymes play important roles in the production of reactive metabolites.[6] Genetic variations in drug-metabolizing enzymes are significantly associated with ATD-induced liver injury.[7] In INH metabolism, slow-acetylator phenotypes are associated with ATD-induced hepatitis, and genetic mutations in *N*-acetyltransferase 2 (NAT2) increase the risk of ATD-induced hepatitis.[8,9] Additionally, an association between *CYP2E1* polymorphisms and ATD-induced hepatitis was reported, although the association was inconsistent in the studied population groups.[10–12]

Glutathione *S*-transferase (GST) is a phase II drug-metabolizing enzyme that catalyzes the conjugation of reduced glutathione

Abbreviations: ALT, alanine aminotransaminase; AST, aspartate aminotransaminase; ATD, antituberculosis drugs; GST, glutathione *S*-transferase; HLA, human leukocyte antigen: INH, isoniazid; MPE, maculopapular eruption; NAT2, *N*-acetyltransferase 2; PCR, polymerase chain reaction; SJS, Stevens Johnson syndrome; TB, tuberculosis; ULN, upper limit of normal.

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(GSH) to various substances. Glutathione acts as an antioxidant and protects cells from injury by scavenging reactive oxygen species and toxic metabolites. Because GST is involved in drug metabolism and the detoxification response, deficiency in GST activity can lead to development of adverse drug reactions. Based on this hypothesis, the relationship has been examined between genetic polymorphisms in GST enzymes and the development of ATD-induced hepatotoxicity. Previous studies in an Indian[13] and a Taiwanese population[14] reported that homozygous null mutations in *GSTM1* increased the risk of ATD-induced hepatitis. In contrast to these findings, a subsequent study in Spain failed to validate this association, reporting instead that null mutations in *GSTT1* were associated with ATD-induced hepatotoxicity.[15] Thus, the association between null mutations of GSTT1 or GSTM1 and ATD-induced hepatitis remains unclear and needs to be replicated in other ethnic groups.

ATD-induced cutaneous reactions, such as rashes, can be serious adverse reactions and their incidence is higher than that of hepatitis and gastrointestinal reactions.[2] Despite the clinical significance of ATD-induced cutaneous reactions, not much is known about genetic predisposition to these reactions. It is suggested that, like drug-induced liver injury, hypersensitivity reactions to reactive metabolites underlie the mechanisms of drug eruption. Langerhans cells and epidermal keratinocytes have been suggested to play pivotal roles in the development of drug-induced hypersensitivity reactions in the skin. Drug metabolites transferred into or bioactivated in the skin can induce an immune response after haptenization.[16] Detoxification by GST enzymes may be involved in the development of cutaneous reactions to ATD. Therefore, we hypothesized that null mutations of GSTT1 and GSTM1 genes are associated with ATD-induced cutaneous reactions. To our knowledge, there is no published report on the association between genetic polymorphisms in GST enzymes and ATD-induced skin reactions. In this study, we examined whether null mutations in GSTT1 and GSTM1 were associated with the development of ATD-induced hepatitis and adverse cutaneous reactions in a Korean population.

2. Methods

2.1. Subjects

This multi-center study was carried out at seven university hospitals in Korea (Dankook University Hospital, Eulji University Hospital, Hanyang University Hospital, Hallym University Hospital, Seoul National University Hospital, Ajou University Hospital, and Seoul National University Bundang Hospital) from July 2003 to October 2008. We prospectively enrolled patients with ATD-induced hepatitis and ATD-induced adverse cutaneous reactions among patients newly diagnosed with pulmonary TB and/or TB pleuritis and treated with first-line anti-TB medications. Before initiating anti-TB treatments, patients underwent a liver function test, complete blood cell count analysis, hepatitis B and C viral marker study, and measurement of serum creatinine and blood urea nitrogen. The exclusion criteria were as follows: (1) abnormal liver function test result at baseline (elevated serum AST, ALT, or bilirubin above normal range); (2) active or chronic hepatitis, including alcoholic hepatitis, fatty liver disease and liver cirrhosis; (3) carriers of the hepatitis B or C virus; (4) heavy alcohol intake; (5) decreased renal function; (6) other chronic medical conditions requiring medication; and (7) patients with skin diseases before treatment. For the 2-month initial phase, patients were given INH (300–400 mg daily), rifampin (450–600 mg daily), ethambutol (600–800 mg daily), and pyrazinamide (1000–1500 mg daily), and doses of each drug were adjusted, depending on the body weight of the subjects. Pyrazinamide was omitted in the subsequent continuation phase for 4 months or more with maintenance of INH, RFP, and EMB. The period of the continuation phase in each patient was determined by the clinician, based on clinical features and treatment response. Treatment response and development of adverse reactions to ATD were evaluated on a regular basis, and unscheduled visits occurred if a new symptom arose. At each visit, patients were questioned and examined regarding adverse reactions to ATD, including skin reactions, and were assessed for hepatitis by measurement of serum levels of aspartate aminotransaminase (AST), alanine aminotransaminase (ALT), and total bilirubin. ATD-induced hepatitis was defined as an elevation in the serum level of ALT or AST >3 times the upper limit of normal (ULN) range ($\leq$40 U/L) during treatment, according to the American Thoracic Society guidelines.[4] ATD-induced cutaneous reactions were defined as the development of any cutaneous symptom or skin lesion after receiving ATD medication. Types of cutaneous reactions were determined by allergists at each hospital. Among the 896 patients with pulmonary TB, 40 were excluded based on exclusion criteria. In a study population of 856 patients, 57 patients (6.7%) developed ATD-induced hepatitis and 94 patients (11.0%) showed ATD-induced cutaneous reactions. We randomly selected control subjects (two times number of case subjects) among patients who showed no adverse reaction to ATD during the treatment period and agreed to participate in this study. There was no significant difference in demographic parameters, such as age, sex, height and weight, and baseline levels of AST, ALT or total bilirubin between case and control subjects.

This study was approved by the Ethics Committee of each participating hospital. Written informed consent was obtained from all enrolled subjects.

2.2. Genotyping of GSTT1 and GSTM1 mutations

DNA was extracted from whole blood using the Genomic PUREGENE® DNA Isolation Kit (Gentra Systems, Inc., Minneapolis, MN, USA). A polymerase chain reaction (PCR) technique that detected homozygous deletions of *GSTT1* and *GSTM1* was used, with primers for the β-globin gene as an internal control. PCR was performed in a 10-μL reaction mixture containing 50 ng of DNA template, 0. units of i-star Taq polymerase (iNtron biotechnology, Korea), and the following primers at 0.5 pM concentration: (forward) 5′-TTC CTT ACT GGT CCT CAC ATC TC-3′ and (reverse) 5′-TCA CCG GAT CAT GGC CAG CA-3′ for *GSTT1,* (forward) 5′-GAA CTC CCT GAA AAG CTA AAG G-3′ and (reverse) 5′-GTT GGG CTC AAA TAT ACG GTG G-3′ for *GSTM1*, and (forward) 5′-GAA GAG CCA AGG ACA GGT AC-3′ and (reverse) 5′-CCA CTT CAT CCA CGT TCA CC-3′ for beta-globin. The following steps were used for amplification: initial denaturation at 95 °C for 10 min, followed by 35 cycles of denaturation at 95 °C for 30 s, annealing at 55 °C for 1 min, extension at 55 °C for 1 min, and an additional cycle at 72 °C for 10 min. The sizes of amplified fragments, visualized on a Ready Agarose 96 plus 3% TBE gel (Bio-Rad, Hercules, CA, USA), were 459 bp for *GSTT1,* 219 bp for *GSTM1,* and 268 bp for β-globin. The absence of an appropriate PCR product for *GSTT1* or *GSTM1,* despite the presence of a product for β-globin was taken to indicate the respective null genotype.

2.3. Statistical analysis

Baseline characteristics of the subjects were compared using the chi-square test for categorical variables and the Mann–Whitney *U* test for continuous variables. Frequencies of null mutations for both genes were compared between case and control groups using multivariate logistic regression analysis, considering age, gender, and baseline serum AST and ALT levels as covariates. Statistical

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