Pharmacogenetics

Polymorphism of PXR gene associated with the increased risk of drug-induced liver injury in Indonesian pulmonary tuberculosis patients

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SUMMARY
What is known and objective: Tuberculosis is still a major infectious disease in Indonesia. Patients are treated mostly using fixed-dose combination treatment in primary public health facilities. The incidence of antituberculosis drug-induced liver injury (AT-DILI) is approximately 10% among Indonesian tuberculosis patients who used standard fixed combination regimens during the intensive phase of treatment. However, information regarding genetic polymorphism associated with the increase risk of drug-induced liver injury is still limited. The aim of this study was to investigate pregnane X receptor (PXR) gene polymorphisms as one of the risk factors of AT-DILI.

Methods: In this prospective cohort study, we recruited 106 adult patients diagnosed with pulmonary tuberculosis and treated with category 1 FDC (fixed-dose combination). The identification of SNP -25385C>T (rs3814055) was conducted by ARMS amplification refractionary mutation system. Hepatotoxicity was defined as ALT and/or AST levels above the normal threshold on the second, fourth and sixth months of monitoring during tuberculosis treatment.

Results and discussion: The logistic regression analysis showed that patients with the TT genotype of PXR gene (rs3814055) significantly had a greater risk of AT-DILI (OR 8.93, 95% CI 3.6–57.93, P < 0.05), compared with those of wild-type CC genotype.

What is new and conclusion: The result suggests that in Indonesian patients with tuberculosis, the risk of having AT-DILI was associated with TT genotype of the PXR gene.

WHAT IS KNOWN AND OBJECTIVE
Tuberculosis (TB) is an infectious disease that is still a major problem in developing countries, including Indonesia. In 2014, the World Health Organization categorized Indonesia as a high-TB-, multi-drug resistant (MDR)-TB-, and human immunodeficiency virus (HIV)-burdened country. There are an estimated 9.0 million incident cases of TB and 1.5 million people died of the disease each year (1.1 million deaths were HIV negative, and 360 000 were HIV positive). The corresponding figures for Indonesia are 325 582, and 7964 cases of TB have been identified as new and relapse cases, respectively.1 Given this high burden of disease, the government of Indonesia is focusing on the control and elimination of TB. One of the efforts is through the directly observed treatment, short-course strategy (DOTS) programme.

One of the main concerns in antituberculosis drugs (ATDs) is drug-induced liver injury (DILI) or hepatotoxicity caused by drugs.2 Of the first-line anti-TB drugs, isoniazid, pyrazinamide and rifampicin can all cause liver damage (drug-induced hepatitis).3 In addition, rifampicin can cause asymptomatic jaundice without evidence of hepatitis.4 A previous publication has shown that the incidence of antituberculosis drug-induced liver injury (AT-DILI) is around 10% among Indonesian TB patients treated with standard fixed combination regimens during the intensive phase of treatment.4 Many researchers have reported on specific gene polymorphisms as risk factors for those hepatotoxic effects. Some of the reported genes are N-acetyltransferase 2 (NAT2),5–10 cytochrome P450 2E1 (CYP2E1),9,11,12 glutathione S-transferase mu-1 (GSTM1)9,10,13 and glutathione S-transferase theta (GSTT).9,13 Other genes also reported to be potential predictors of ATDs-DILI are pregnane X receptor (PXR), glutathione S-transferase alpha-1 (GSTM1), manganese superoxide dismutase (MnSOD, SOD2), UDP-glucuronosyltransferase (UGT), nitric oxide synthase 2A (NOS2A), BTB and CNC homology 1 (BACH1), Maf basic leucine zipper protein (MAFK), and human leucocyte antigen (HLA).14–18

We examined PXR gene polymorphism because lignand formation between rifampicin and PXR could trigger the expression of various genes, including various cytochromes and carboxylesterases that may be relevant to the metabolism of isoniazid in producing hepatotoxic metabolites. PXR plays a role in the regulation of a number of hepatic and intestine genes involved in detoxification and elimination of xenobiotics.19 The polymorphisms are generally located in the 5′-flanking region of the target genes.20 PXR activates various genes through binding and heterodimer formation with the retinoid X receptor (RXR). PXR ligands stimulates the expression of genes involved in xenobiotics oxidation (phase I), conjugation (phase II) and transport (phase III) in the liver. PXR is involved in phase I metabolism through the expression of CYP2B6, CYP2C8, CYP2C9, CYP2B9 and CYP2C19.21–25 Moreover, PXR is involved in phase II metabolism through the expression of glutathione S-transferase (GST), sulfortransferase, UDP-glucuronosyltransferase and carboxylesterase.26–31 PXR is involved in phase III through the expression of