Hubungan Variasi Genetika *NAT2* Terhadap Risiko *Adverse Drug Reaction* (ADR) dan *Outcome* Klinis Pasien Tuberkulosis Suku Jawa

INTISARI

Polimorfisme *NAT2* berkaitan dengan risiko ADR dan efektivitas pengobatan. Penelitian polimorfisme *NAT2* pada suku Jawa dengan sistem penelusuran 3 riwayat etnis belum pernah dilakukan, penelitian tentang hubungan *NAT2* dengan ADR hepatotoksisitas telah banyak dikerjakan namun terhadap ADR neurologi dan dermatologi belum banyak dikaji. Tujuan penelitian adalah mengidentifikasi polimorfisme *NAT2* dan mengevaluasi hubungannya dengan ADR dan *outcome* klinis.

Penelitian dilakukan secara prospektif terhadap 33 responden suku Jawa, dan mendapat terapi Obat Anti Tuberkulosis (OAT) kategori 1, metode penelitian adalah *cross sectional.* Identifikasi polimorfisme *NAT2* dilakukan dengan metode *Polimerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP)*, Monitoring ADR dilakukan dari bulan ke-2 hingga bulan ke-6 pengobatan, pemeriksaan SGPT/SGOT dilakukan pada bulan ke-2 pengobatan, *outcome* klinis diamati pada akhir pengobatan. Analisis hubungan genotip dengan ADR dilakukan dengan analisis *bivariate chi-square*, analisis hubungan genotip dengan outcome klinis dilakukan menggunakan analisis *multivariate regresi multinomial*.

Hasil penelitian menunjukkan terdapat polimorfisme gen *NAT2* dengan persentase mutasi pada 3 SNP yaitu C481T, G590A, dan G857A sebesar 27%, 54%, dan 31%. persentase jumlah allel *NAT2*4, NAT2*7, NAT2*6, NAT2*5* sebesar 36.8%, 27.6%, 22.4%, dan 11.8%. Secara trimodal terdapat 3 kelompok prediksi fenotip yaitu tipe *fast* acetylator, *intermediate*, dan *slow acetylator* sebesar 6%, 76%, dan 12%. Tidak dijumpai adanya ADR hepatotoksisitas pada seluruh subyek, ADR yang timbul adalah gangguan gastrointestinal, dermatologi dan neurologi sebanyak 36,4%, 9%, dan 27%. Secara statistik tidak terdapat hubungan antara genotip dengan ADR (*p-value* =0,324>0,05) dan outcome klinis (*p-value* = 0,581>0,05) namun berdasar fenomena klinis ADR yang timbul serta temuan allel NAT2*6 dan *7 dalam persentase tinggi maka hasil penelitian ini dapat menjadi informasi perlunya monitoring ADR pada pasien suku Jawa.

Kata kunci : Polimorfisme *NAT2*, Genotip *NAT2*, Isoniazid, ADR Obat Anti Tuberkulosis

The Relationship of *NAT2* Genetic Variations to the Risk of Adverse Drug Reaction (ADR) and Clinical Outcome Javanese Tuberkulosis Patients

ABSTRACT

NAT2 polymorphisms are associated with ADR risk and treatment effectiveness. Research on NAT2 polymorphism in Javanese with a 3 ethnic history tracing system has never been carried out. Research on the relationship between NAT2 and ADR hepatotoxicity has been done a lot, but neurological and dermatological ADR has not been widely studied. The study aimed to identify NAT2 polymorphisms and evaluate their association with ADR and clinical outcomes.

The study was conducted prospectively on 33 Javanese respondents and received category 1 Anti-Tuberculosis Drug (OAT) therapy. The research method was cross-sectional. Identification of NAT2 polymorphisms was carried out by the Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) method, ADR monitoring was carried out from the 2nd to 6th month of treatment, SGPT / SGOT examinations were carried out at the 2nd month of treatment, clinical outcomes were observed. at the end of treatment. Analysis of the relationship between genotypes and ADR was carried out using bivariate chi-square analysis.

The results showed that there was a NAT2 gene polymorphism with the percentage of mutations in 3 SNPs, namely C481T, G590A, and G857A of 27%, 54%, and 31%. the percentage of allele NAT2 * 4, NAT2 * 7, NAT2 * 6, NAT2 * 5 was 36.8%, 27.6%, 22.4%, and 11.8%. In trimodal, there were 3 groups of phenotypic predictions, namely the fast (rapid) acetylator, intermediate, and slow acetylator types of 6%, 76%, and 12%. There were no hepatotoxicity ADRs in all subjects, ADRs that arose were gastrointestinal, dermatological, and neurological disorders as much as 36.4%, 9%, and 27%. Statistically, there is no relationship between genotype with ADR (p-value = 0.324> 0.05) and clinical outcome (p-value = 0.581> 0.05) Clinically, the high percentage of NAT2 * 6 and * 7 alleles as predictor alleles of ADR, as well as the clinical phenomenon of ADR that appears to provide information that Javanese tuberculosis patients need ADR monitoring during tuberculosis treatment.

Key words : **NAT2 Polymorpishm, Genotype NAT2, Isoniazid, ADR of Antituberculosis Drugs**