ABSTRAK

Latar belakang: Sebanyak 40% pasien tidak memperoleh efek terapi yang optimal pada awal penggunaan metformin sebagai monoterapi DM tipe 2. Hal tersebut dapat disebabkan oleh variasi gen *SLC22A1* rs628031 pada transporter OCT1.
Tujuan: Studi ini bertujuan untuk mengetahui pengaruh variasi genetik *SLC22A1* rs628031 Met408Val pada OCT1 terhadap farmakokinetik/farmakodinamik metformin.
Metode penelitian: Penelitian ini bersifat observasional dengan rancangan *cohort* prospektif pada 123 pasien DM tipe 2 yang menggunakan monoterapi metformin 2x500 mg. Variasi genetik *SLC22A1* rs628031 Met408Val dianalisis dengan metode PCR-RFLP. Pengembangan dan validasi metode penetapan kadar metformin dalam plasma dilakukan dengan metode HPLC-UV. Parameter FK/FD berbasis data populasi yang ditetapkan meliputi ka, Vd, k, Css_{maks}, Css_{min}, AUC, T_{mak}, Cl, t ½, Cc0, R0, IC_{50}, k_{in}, k_{out} menggunakan software *monolix* versi 2023R1 dengan pendekatan metode *indirect response model*. Analisis pengaruh variasi genetik terhadap kadar HbA1c, glukosa darah puasa (GDP), glukosa darah 2 jam postprandial (G2PP) dilakukan dengan membandingkan perubahan nilai *baseline* dengan minggu ke-12. Analisis pengaruh kovariat seperti *body mass index* (BMI), usia, jenis kelamin, kliren kreatinin, GFR, kepatuhan pengobatan dianalisis dengan strategi COSSAC *covariate model monolix* versi 2023R1 dan uji regresi linier. Uji statistika dinyatakan bermakna pada ($p < 0,05$).
Hasil: Hasil identifikasi variasi genetik SLC22A1 rs628031 Met408Val dari 123 responden menunjukkan frekuensi kelompok *allele* AA sebesar 14% dan *allele* AG-GG sebesar 86%. Pemodelan FK/FD metformin berbasis populasi menunjukkan fitting kurva yang baik dengan pendekatan *indirect response model*. Kelompok *allele* AG-GG mengalami penurunan nilai ka, Vd, t ½, k_{in}, k_{out} dan mengalami peningkatan parameter Css_{maks} dan k ($p<0,05$). Kelompok *allele* AG-GG juga mengalami penurunan parameter HbA1c, GDP dan G2PP yang lebih rendah jika dibandingkan dengan kelompok *allele* AA($p<0,05$).
Kesimpulan : Variasi genetik SLC22A1 rs628031 Met408Val menurunkan nilai ka, Vd, t ½, k_{in}, k_{out} , meningkatkan nilai Css_{maks} dan k, serta menurunkan respon terapi metformin berdasarkan parameter HbA1c, GDP dan G2PP.

Kata kunci: Metformin, DM tipe 2, *SLC22A1* rs628031, farmakokinetik/farmakodinamik populasi, *indirect response model*.

ABSTRACT

Background: Up to forty percent of individuals do not attain maximum therapeutic outcomes when using metformin as a standalone treatment for diabetes. Genetic variations in the OCT1 transporter gene SLC22A1 rs628031 can lead to this condition.
Objective: The objective of this study is to investigate the impact of the genetic polymorphism SLC22A1 rs628031 Met408Val in OCT1 on the pharmacokinetics/pharmacodynamics of metformin.
Method : This study was conducted on 123 individuals with type 2 diabetes mellitus who were receiving metformin monotherapy at a dosage of 2x500 mg. The genetic variant of SLC22A1 rs628031 Met408Val was examined using PCR-RFLP. The HPLC-UV method was employed to validate and optimize the procedure for quantifying metformin levels in plasma. Population PK/PD parameters include ka, Vd, k, Css_{max}, Css_{min}, AUC, T_{max}, Cl, t ½ , R0, Cc0, k_{in}, and k_{out}, calculated using Monolix software version 2023R1 using indirect response model method structure. The impact of genetic variations on HbA1c levels, fasting blood glucose (FBG), and fasting blood glucose after 2-hour postprandial (FBG2PP) was analyzed by comparing baseline to 12-week changes in values. The influence of covariates, including body mass index (BMI), age, gender, creatinine clearance, GFR, and treatment adherence, was analyzed using the COSSAC covariate model monolix version 2023R1 and linear regression testing. At ($p< 0.05$), the statistical test was deemed significant.
Result: Identifying the genetic variation SLC22A1 rs628031 Met408Val in 123 respondents revealed a frequency of 14% in the allele AA group and 86% in the allele AG-GG group. Using the indirect response model approach, population-based PK/PD modeling of metformin reveals decent curve fitting. The parameters ka, Vd, t ½, k_{in}, and k_{out} decreased in the allele AG-GG group, while Css_{max} and k increased ($p< 0.05$). HbA1c, FBG, and FBG2PP parameters decreased less in the allele AG-GG group compared to the allele AA group ($p< 0.05$).
Conclusion: The genetic variation SLC22A1 rs628031 Met408Val reduces ka, Vd, t ½, k_{in}, and k_{out} values, increases Css_{max} and k, and decreases the response to metformin therapy, based on HbA1c, FBG, and FBG2PP parameters.

Keywords: Metformin, DM type 2, SLC22A1 rs628031, population pharmacokinetics/pharmacodynamics, indirect response model.