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ABSTRACT

Pharmacogenetic control of clopidogrel treatment response

Cardiovascular diseases, especially coronary artery disease, are the leading cause of death worldwide. The main purpose of treatment is to prolong and improve the quality of life. Clopidogrel is part of the protocol for treatment of Coronary artery disease, Peripheral artery disease and vertebrobasilar disease. It is a prodrug that acts as an inhibitor of platelet aggregation and exerts pharmacological action by binding irreversibly to the P2Y12 receptor and inhibits the binding of ADP, thus inhibiting the activation of the glycoprotein GpIIb/IIIa receptor and inhibiting platelet aggregation. After absorption from the gastrointestinal system, the drug undergoes two CYP450 mediated oxidative processes in order to be converted into the active form. In the first phase of oxidation clopidogrel is converted to the intermediate metabolite 2-oxoclopidogrel, while in the second phase to its thiol metabolite. The major enzyme involved in the clopidogrel bioactivation is CYP2C19 (1,2). Relatively high incidence of Major Adverse Cardiovascular and Cerebrovascular Events (MACCE) observed in cardiovascular patients, despite ongoing antiplatelet therapy has prompted several studies evaluating risk factors associated with clopidogrel treatment failure (3).

Genetic variation in the regulation, expression and activity of genes coding for Phase I, Phase II drug metabolizing enzymes (DMEs) and drug targets, can be defining factors for the variability in both the effectiveness and occurrence of drug therapy side events. From clinical studies conducted it has been observed that interindividual variability and MACCE are associated with CYP2C19 genetic variations that could lead to reduced or potentiated enzymatic function. The most important variants that determine the metabolism of clopidogrel and affect the treatment outcome are: CYP2C19 * 2 loss of function allele, the CYP2C19 * 3 loss of function and CYP2C19 * 17 gain of function allele (3,0). However, the known CYP2C19 polymorphisms faild to account for all observed interindividual differencies and phenotypes related to clinical clopidogrel response. Recently published study by Kapedanovska et al., (2019)., suggests that AKR1D1* 36 (rs1872930) allelic variant is independently associated with clopidogrel treatment outcome. AKR1D1 gene is thought to have a role as a trans genetic regulator of the enzymatic system cytochrome P450The AKR1D1*36 allele enhance the expression of the mRNA hepathic CYP450 which in turn increase the enzimatic activity of CYP2C19 responsible for metabolism of clopidogrel, therefore is belived that this allele has an impact on the oocurrence of the adverse effects during the therapy with the antagonist of the P2Y12 receptor (4). Regarding the contribution to previous knowledge (4,5,6), it is still unclear whether the AKR1D1*36 C>T (rs1872930) allelic variant influences CYP2C19 enzyme activity (i.e. catalytic activity, kinetics), or the expression of CYP2C19 mRNA, and consequently enzyme activity, or AKR1D1 has its own enzymatic activity in the clopidogrel biotransformation associated with the therapeutic outcome. Additionally, information regarding the geographic structure and multi-ethnic distribution of clinically relevant genetic variations is becoming increasingly useful for improving drug therapy and explaining inter-individual and inter-ethnic differences in drug response (7). Krasniqi at al., (2017)., in their study determined the frequency of variant alleles of CYP2C19 in Kosovo population, found that the CYP2C19 gene polymorphisms are similar to the other European population and the most frequent alleles were CYP2C19*2 and CYP2C19*17(8). However, the frequency of AKR1D1*36 allelic variant is still unknown.

The purpose of this study is to answer all the above questions of broader biological relevance with focus on the possible role of AKR1D1enzyme in the metabolism and clopidogrel treatment outcome in patients from Kosovo. The study will include max. 100 patients with coronary artery disease (CAD) who have indication and start with clopidogrel and fulfill the predefined specific inclusion / exclusion criteria. The study will be conducted according to Declaration of Helsinki code of ethics. All subjects will be evaluated on CYP2C19 and AKR1D1 genetic status using the Real Time PCR method. The patients pharmacogenetic profile will be linked to the their clopidogrel pharmacokinetic profile. Clopidogrel

active metabolite in human plasma will be determined using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods.

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