Relationship Between ABCB1 and ABCG2 Genetic Polymorphism and Resistance To Clopidogrel Treatment After Percutaneous Coronary Intervention

M. Ferrari[1], M Tozzi[1], F. Marino[1], M. Mirabile[1], C. Novy[1], A. Tarallo[1], F. Riva[1], P. Castelli[1], M. Cosentino[1]

[1]Center of Research in Medical Pharmacology, University of Insubria, Varese, Italy

Introductions. Dual antiplatelet therapy using aspirin and an ADP receptor blocker is the standard approach to prevent thrombotic complications of percutaneous coronary interventions (Mehta et al., 2001). Among ADP receptor blockers, clopidogrel is one of the most frequently prescribed drugs worldwide. However, the response to clopidogrel varies substantially between patients (Gurbel et al., 2003), and individuals with poor response to clopidogrel are at increased risk of cardiovascular events (Patel et al., 2003). The mechanisms leading to a poor response to clopidogrel have not yet been fully elucidated and are most likely multifactorial, including genetic variability of proteins involved in clopidogrel disposition (Wiviott et al., 2004). For instance, intestinal absorption of clopidogrel is brought about by P-glycoprotein (ABCB1) and individuals with genetic variants in ABCB1, leading to impaired transport, have reduced concentrations of the active drug metabolite and increased rates of adverse clinical outcomes (Carlquist et al., 2013). However, the role of single nucleotide polymorphisms (SNPs) in genes encoding transporter protein in predicting clopidogrel therapy outcome remains to be established.

Aims. The aim of present work is to correlate response to clopidogrel therapy with common single nucleotide polymorphisms (SNPs), alone or in combination, in genes for ABCB1 and ABCG2, which are involved in clopidogrel transport.

Methods. Starting from January 2012, we included in a prospective longitudinal protocol all the patients undergoing percutaneous coronary intervention and subsequently treated with clopidogrel for at least 10 days with the same treatment regimen.

Patients were screened for the occurrence of serious adverse drug reactions (ADR, defined as any clopidogrel-related adverse event leading to drug discontinuation) or failure of clopidogrel therapy defined as clinical diagnosis of thrombosis. Resistance to clopidogrel was assessed by using platelet functional VerifyNow P2Y12 test (Godino et al., 2008).

Patients were genotyped for selected ABCB1 (C3435T, C1236T and G2677T) and ABCG2 (C421A) SNPs by Real Time PCR on an Applied Biosystems GeneAmp 9700 PCR System using a pre-designed genotyping assay (Applied Biosystems, Foster City, California, USA).

Allelic combination analysis was performed by assigning an arbitrary score of +1 to each allele associated with high transport rate and -1 to each allele associate with low transport rate. Subjects were then grouped into: slow transporters (ST – all combinations which gave a score ≤ -2) and rapid transporters (RT - all combinations which gave a score > -2).

Results. So far were enrolled 51 patients treated with clopidogrel, including 5 patients who showed failure of clopidogrel therapy and 8 with ADR leading to drug discontinuation. It was not possible to establish associations between single SNPs and either therapeutic failure or ADR. However, a significant association was found between therapeutic failure and ST genotype combinations, with an O.R. of 8,0 (P = 0,022).

Conclusion. Preliminary results show that genetic variations in key genes for clopidogrel transporters influence treatment outcome, and support the hypothesis that allelic combination analysis allows better prediction of treatment outcome in comparison to individual SNPs. Cost-effectiveness evaluation of this pharmacogenetic approach will establish its role in the routinary assessment of patients undergoing percutaneous coronary intervention and receiving clopidogrel.

References

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