Relationship Between Statin-Related Creatine Kinase Elevations and Genetic Polymorphisms of ABCB1, ABCG2 and SLCO1B1 Transporters

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Introduction. Statins are widely prescribed medications which effectively reduce cardiovascular mortality, however large interindividual variability exists and myopathy is a relatively common adverse effect of these drugs, while severe cases of rhabdomyolysis are rarer but have significant mortality rates (Graham et al., 2004). Established guidelines for prevention of statin-induced muscle damage include measurement of serum creatine kinase (CK) and CK levels > 3 x upper normal limits (ULN) being associated with significantly increased risk of muscle damage (Baker et al., 2008).
Statin-induced muscle damage increases along with increased statin plasma levels (Graham et al., 2004), which in turn are affected by specific intestinal and hepatic transporters such as: organic anion transporting polypeptide 1B1 OATP1B1 coded by SLCO1B1 gene; Breast Cancer Resistance Protein (ABCG2) and P-glicoprotein (ABCB1) (Niemi et al., 2010). Genetic variants in SLCO1B1 have been associated with reduced OATP1B1 activity resulting in increased statin bioavailability and risk of simvastatin-induced myopathy (Santos et al., 2012). Single nucleotide polymorphisms (SNPs) in the ABCB1 gene have been associated with higher risk of statin-induced myalgia (Hoenig et al., 2011). However, no studies so far addressed the combined effect of SNPs in the various transporters on the risk of statin-induced CK elevation and myalgia.
Aims. The present study was devised to test the hypothesis that SNPs in statin transporter genes leading to a low transporter phenotype may be a predisposing factor for statin-induced CK elevations. To this end, we compared the genetic profile of the main transporters involved in statin disposition in dyslipidemic patients treated with statins with or without CK elevations.
Methods. Patients of both sexes treated with statins and showed statin-related CK elevations > 3 x UNL were consecutively enrolled. Sex-, age- and therapy- matched consecutive patients without CK elevations were taken as controls. Patients were genotyped for selected ABCB1, ABCG2 and SLCO1B1 SNPs by Real Time PCR on an Applied Biosystems StepOne System using a pre-designed genotyping assay (Applied Biosystems, Foster City, California, USA).
SNPs in ABCB1 and SLCO1B1, were combined into functional categories based on published descriptions of the alleles or genotypes. We defined an arbitrary score by assigning +1 to each allele associated with high transport rate and -1 to each allele associate with low transport rate. Genotype combinations were then grouped into: high statin effusion (HE: all combinations which gave a score >0), low statin effusion activity (LE: all combinations which gave a score ≤0).
Results. We identified 33 consecutive patients (13 male/20 female; age: 62,1±9,9 years) on treatment with statins showing CK elevations and 33 matched controls (13 male/20 female; age: 61,2±9,9 years). Increased risk of CK elevations was associated with ABCB1 1236T/T and 3435 T/T genotypes, with an odds ratio (OR) of 4,6 (P = 0,007) and 3,2 (P = 0,049), respectively. Moreover the frequency of CK elevation was significant higher in patients with SLCO1B1 521C/C with an OR of 8,8 (P = 0,02). When patients were grouped according to the functional activity of genotype combinations, we found that LE subjects showed higher risk of statin-induced CK elevations with and OR of 10,4 (P < 0.0001).
Conclusion. Genetic variations in key genes for statin transporters are associated with the risk of CK elevation during statin treatment. Results support the hypothesis that allelic combination analysis allows better prediction of treatment outcome in comparison to individual SNPs.

References

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