Pharmacogenetics/Pharmacogenomics/Personalized medicine

Cod: 1356

ASSESSING THE HIGH ON-TREATMENT PLATELET REACTIVITY (HPR) AND RISK OF BLEEDING WITH MULTIPLE ELECTRODE IMPEDANCE AGGREGOMETRY (MEA) IN PATIENTS USING CLOPIDOGREL, PRASUGREL AND TICARGELOR

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BACKGROUND: High on-treatment platelet reactivity (HPR) is independent risk factor for early stent thrombosis (ST). The purpose of this study was to evaluate the effect of P2Y12 receptor inhibitors - clopidogrel, prasugrel and ticagrelor, on residual hight platelet reactivity, as well as, the risk of bleeding.

METHODS: Platelet function was assessed with MEA in whole blood on Multiplate analyzer. Adequate response to ADP P2Y12 receptor blocking medication was defined as ADP-test > 450 AU, on the base of cut-off value, determined by ROC analysis (area under the curve was 0.864, with 0.84 specificity and 0.78 sensitivity). Blood samples were drawn into tubes containing hirudin at least 14 h after loading or 3-5 days after maintaining doses. We studied 204 patients, 120 of them are on 150 mg/d clopidogrel, 54 patients were on 10 mg/d prasugrel and 30 patients on 2 x 90 mg/d ticagrelor. We also obverse the hyper response to P2Y12 receptor inhibitors, defined as ADP-test > 180 AU.

RESULTS: 90 out of 120 patients with HPR (75 %) showed normal response on doubling (150 mg) maintaining dose of clopidogrel (ADP 343 ±127 AU). ADP P2Y12 receptor blocking was not sufficient in 30 (25 %) of the patients (ADP 675 ±143 U) and thienopyridine treatment was switched to prasugrel 10 mg daily. Out of 54 patients on prasugrel 10 mg/ daily (ADP 262 ±120 AU), four patients (7.5%) required 15 mg daily to reach optimal level of ADP-inhibition (273±550 AU). In patients group on ticagrelor treatment (ADP-test 227 ±154 AU), two patients with diabetes mellitus had no adequate inhibition (ADP-test 58 and 69 AU, resp.) and were switched on prasugrel (ADP-test 34 AU and 37 AU). We found minor bleeding complications like cutaneous hematoma, epistaxis, haemorrhoidal bleeding, and hemoptoe in 0.6% of patients with lower values of ADP test (121 ± 52 AU).

CONCLUSIONS: We found impaired response to prasugrel in 4 of 54 (7.4%) and in two of 30 (6.7%) patients on ticagrelor. ADP-test < 18 U was associated with increased risk of minor bleeding.

Pharmacogenetics/Pharmacogenomics/Personalized medicine

Cod: 1357

EFFECT OF CYP3A4*22 POLYMORPHISM ON DOSE ADJUSTMENT OF TACROLIMUS IN HEPATIC TRANSPLANT

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BACKGROUND: Polymorphisms in genes encoding drug biotransforming enzymes, like cytochrome P450 isoenzymes, can play an important role in the variability of the metabolism of immunosuppressive drugs. It has been described that patients harboring the CYP3A4*22 variant have a lower capacity for tacrolimus metabolization.
The aim of this study was to evaluate the impact of CYP3A4*22 polymorphism on plasma concentrations and dose management of tacrolimus (Tac) in patients with liver transplantation, according to the genotype of both the liver recipient and donor.

METHODS: An observational retrospective single-center study was performed. Patients who underwent a primary liver transplant treated with Tac, were selected according to defined criteria. Plasma Tac levels were measured in the IMX® analyzer (Abbott). DNA was extracted from peripheral blood lymphocytes in recipients (n=65) and from paraffin embedded gallbladder samples in donors (n=67). The presence of the CYP3A*22 variant was assessed by real-time PCR using allele-specific probes (Life Technologies). Patients were classified as CYP3A4*1/*1 (wild type) or CYP3A4*1/*22 (15389C>T) (carriers). Concentration, dose and the concentration/dose ratio data were collected at days 3, 7, 14, 30 and 90 post-transplant. Analysis of these variables per day and the accumulated data of each variable are described.

RESULTS: Wild type allele frequency was higher in both recipients (87.7 % vs 12.3 %) and donors (82.1 % vs. 17.9). Donor genotype was not found to influence any of the variables. In recipient carriers, the concentration/dose ratio was higher in all of the days studied. The accumulated data showed differences between carriers and non-carriers that tend to significance in case of concentration/dose ratio (p=0.063) and significant differences (p=0.033) were found on Tac concentration, confirming that CYPA4*22 -carriers present a higher drug accumulation.

CONCLUSIONS: Patients with CYP3A4*22 variant reach higher Tac plasma concentrations, probably requiring lower doses of the drug. Studies with larger sample size, and the analysis of other polymorphisms, would help to improve the immunosuppressive treatment, with the potential to prevent their severe side effects and/or the organ rejection.

Pharmacogenetics/Pharmacogenomics/Personalized medicine

Cod: 1358

MEASUREMENT OF ANTI-TNF DRUGS LEVELS IS THE KEY TO OPTIMAL, PERSONALIZED AND COST-EFFECTIVE TREATMENT

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BACKGROUND: Monoclonal antibodies targeting tumor necrosis factor (TNF) have proved to be powerful drugs. Biologicals are among the most expensive drugs available. As accuracy and reproducibility are vital in these assays, we have developed and standardized anti-TNF drug monitoring assays with high precision and robustness and show that these assays can be applied to provide patients with optimal individual treatment in a cost-effective manner.

METHODS: In a prospective observational cohort study, 221 consecutive patients with rheumatoid arthritis (RA) were treated with adalimumab (Humira™) subcutaneously every other week. Drug levels were measured and the relationship between adalimumab trough level and clinical efficacy after 28 weeks of follow-up was determined.

RESULTS: Clinical efficacy (determined by DAS score) improved with increasing adalimumab concentration and reached a maximum with levels between 5–8 μg/mL. Levels exceeding 8 μg/mL were illustrated to have no additional beneficial effect on disease activity. The ROC curve showed an area under the curve of 0.695 (95% CI 0.626 to 0.764) for European League Against Rheumatism response and adalimumab levels: good responders versus non-responders and moderate responders. A cut-off of 5 μg/mL had a sensitivity of 91% and a specificity of 43%.

CONCLUSIONS: We propose a personalized medicine approach that benefits the patient and prevents over treatment or treatment with an ineffective drug, both leading to a more cost-effective treatment of patients. In patients with levels higher than necessary, drug dosing may be reduced without loss of efficacy of the drugs. Measuring antidrug antibodies (ADA) in patients with low serum drug levels, aids in clinical decision making. Patients not responding to therapy, with low drug levels and ADA formation, may switch therapy with other anti-TNF drugs. In contrast, non-responders with adequate drug levels who do not develop ADA may benefit from biologicals with another mode of action.

Pharmacogenetics/Pharmacogenomics/Personalized medicine

Cod: 1359

IMPACT OF GENETIC AND NON-GENETIC FACTORS ON WARFARIN RELATED BLEEDINGS IN TURKISH PATIENTS

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BACKGROUND: The CYP2C9 is one of the clinically important drug metabolizing enzymes that demonstrate genetic variations with significant phenotype and clinical outcomes. The patients with CYP2C9*2 and *3 variants need a longer time to reach the warfarin maintenance dose and are at higher risk of serious and life-threatening bleeding. In this study we investigate the impact of the CYP2C9 polymorphisms (*1, *2 and *3) and other personal characteristics on warfarin dose requirements in Turkish patients.

METHODS: A total of 189 unrelated patients with (n=92 cases) and without (n=97 controls) hemorrhagic complications during warfarin therapy was consecutively enrolled. MALDI TOF based Sequenom MassARRAY platform was used for genotyping process. Using multiple statistical analyses different variables were considered separately to assess their impact on warfarin dose adjustment, hemorrhage risk, and its severity.

RESULTS: Determined genotype frequency among all the subjects were 0.69, 0.18, 0.11 for CYP2C9*1*1, 1*2, 1*3, respectively. The cases and the controls did not have a significant difference in terms of wild type (*1*1) and polymorphic variant (*1*2, *1*3) distribution. CYP2C9*1*2 and *1* 3 variants were associated with 12.9% and 17.6% of dose variability. Combined effect of genotype and age on the severity of hemorrhagic complications were analyzed and significant association was determined (p=0.01). Contribution of genotype and age to warfarin dose requirement was defined as 24.4%. The results of logistic regression model showed that aspirin usage during warfarin therapy increases the risk of hemorrhage by <0.2 for therapeutic and >0.2 for supratherapeutic INR range. Gastrointestinal system (GIS) was a common hemorrhage point accounting for 35.8% of the cases, and 72.7% of them had life threatening hemorrhage (p=0.01).

CONCLUSIONS: Present data provides an insight into the common CYP2C9 variants in Turkish patients, clarifying a relationship of genetic background with different personal characteristics and the clinical use of warfarin. Our results will useful to improve algorithms such as initial warfarin dose adjustment and better prediction of anticoagulation response outcomes.

Pharmacogenetics/Pharmacogenomics/Personalized medicine

Cod: 1360

COMPLETE SEQUENCE-BASED SCREENING OF TPMT VARIANTS

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BACKGROUND: Thiopurine S-methyltransferase (TPMT) is a cytoplasmic enzyme involved in the metabolism of thiopurine drugs. Patients with impaired TPMT activity are at risk for myelosuppression related to thiopurine therapy. TPMT activity is largely influenced by polymorphisms of the TPMT gene. To date, more than 30 variants in TPMT are known to be associated with reduced enzyme activity. However, most studies on the TPMT genotype have been included only common nonfunctional variants, TPMT*2 and TPMT*3. We performed complete sequencing analysis to screen all TPMT variants in the Korean patients.

METHODS: Total 900 Korean patients were genotyped for TPMT. Peripheral blood specimens were collected and genomic DNA was extracted. To identify all TPMT variants, direct sequencing assay for all 8 coding exons and intron-exon boundaries of the TPMT gene was performed. Cycle sequencing was performed by ABI 3130xl Genetic Analyzer (Applied Biosystems, Foster City, CA, USA).

RESULTS: Of the 900 Korean patients, 28 patients (3.2%) had variant alleles. TPMT*3C (c.719A>G, rs1142345) was found in 25 cases (2.8%); 24 cases with TPMT*1/*3 and one with TPMT*3/*3. Rare TPMT variants including TPMT*6 (c.A539T, rs75543815), TPMT*16 (c.488G>A rs144041067) and TPMT*32 (c.340G>A, rs115106679) were also detected (3 cases, 0.3%). Allele frequencies of TPMT*3C, TPMT*6, TPMT*16, and TPMT*32 were 1.44%, 0.06%, 0.07% and 0.07%, respectively. Thirteen patients with heterozygous TPMT variant were treated with 10~67% of standard dosage of thiopurines. One patient with TPMT*3/*3 required a dosage reduction to 5% of standard dosage.

CONCLUSIONS: This is the first complete sequence-based screening study evaluating all TPMT variants in Asian populations. TPMT*3C was the most common TPMT variant but other rare variants (TPMT*6, TPMT*16 and TPMT*32) were also identified.
Keywords: TPMT, genotype, sequencing, Korean

Pharmacogenetics/Pharmacogenomics/Personalized medicine

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CYP2C9 AND VKORC1 GENOTYPES AND ANTICOAGULATION CONTROL IN PATIENTS WITH HIGH SENSITIVITY TO ACENOCOUMAROL

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BACKGROUND: The object of this study was to assess effects of CYP2C9 (*2/*3) and VKORC1 (1173C>T) genotypes to dose requirement, time in therapeutic range, and risk for overdose in patients with higher susceptibility to acenocoumarol treatment.

METHODS: Genotyping (CYP2C9*3, CYP2C9*2, and 1173C>T in VKORC1) was performed on whole blood EDTA-samples using Verigene Warfarin Metabolism Nucleic Acid Test Kit (Nanosphere, Inc., Northbrook, IL, US). Anticoagulation response was followed for 300 days.

RESULTS: Our previous study on CYP2C9 genotype by real-time PCR in a group of 130 patients shows frequency of CYP2C9*2 (430C>T) and *3 (1075A>C) of 0.16 and 0.07, respectively. Genotyping with Verigene system of a subset of 20 patients requiring low acenocumarol dose (≤1.0 mg/d) reveals that patients who carry CYP2C*1/*3 combined with VKORC1 C/T or T/T (n=6) require 0.795 mg/d, whereas CYP2C*3/*3 combined with VKORC1 C/T or T/T (n=3) require 0.400 mg/d. Time in therapeutic range (TTR) for those patients (n=9) is 46.2%. Percentage of time with overresponse to acenocoumarol treatment (INR >4.0) is 34%, found in 6 out of 9 patients. Homozygous patients with CYP2C9 1*/1* combined with VKORC1 C/T (n=3) or T/T (n=4) require acenocoumarol doses of 0.83 mg/d and 0.868 mg/d, respectively; time in therapeutic range for this subgroup is 53.3% and 25.8% of time with overresponse with INR > 4. The patients, carriers of allele CYP2C9 *2 combined with VKORC1 C/T or T/T genotype (n=4), require 0.715 mg/d acenocoumarol, TTR - 64.4% and 11% with INR > 4.

CONCLUSIONS: Carriers of VKORC1 C/T or T/T combined with CYP2C9 *3/3* require the lowest dose of acenocumarol and are susceptible to over anticoagulation.

Pharmacogenetics/Pharmacogenomics/Personalized medicine

Cod: 1362

COST-EFFECTIVENESS ANALYSIS OF HLA-B*5701 GENOTYPING IN THE PREVENTION OF HYPERSENSITIVITY TO ABACAVIR IN HIV+ PATIENTS

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BACKGROUND: Several pharmacogenetics studies have shown a direct link between the presence of human leukocyte antigen (HLA)-B*5701 and the risk to develop a hypersensitivity reaction to abacavir (ABC).Our aim is to carry out an analysis of cost-effectiveness to evaluate the impact of the systematic HLA-B*5701 genotyping to prevent a possible suspicious hypersensitivity reaction (SHSR) in patients who have been treated with ABC.

METHODS: The cost-effectiveness analysis was assessed by means of a decision tree model with a time horizon of 6 months and two alternatives: systematic and not systematic HLA-B*5701 genotyping.SHSR incidence in each alternative was estimated over retrospective data evaluating two patient cohorts before (2000-2007 years, n=780 patients) and after (2008-2013 years, n=473 patients) systematic HLA-B*5701 testing implementation. HLA-B*5701 prevalence was calculated on the latter cohort. Costs for pharmacologic treatment, HLA-B*5701 test and SHSR treatment were based on our hospital 2013 rates. The software TreeAge Suite Pro 2007 was used to perform the analysis.All the results are expressed per 1000 patients.

RESULTS:HLA-B*5701 prevalence in the genotyped cohort is 5,4%. SHSR incidences in the genotyped and not genotyped groups are 2.1 and 50.0 cases. Using this data as input for the decision tree model, the resulting cost to perform or not the HLA-B*5701 test is €2,095,000 and €2,079,000 respectively. Consequently, the systematic HLA-B*5701 genotyping avoids 47,9 SHSR and a cost increment of €16,000, which supposes an additional cost per HSRS avoided of €334. On the other hand, ABC treatment is cheaper than tenofovir, the main antiretroviral alternative (342 vs 417 €/patient/month) and its prescription has been increasing in recent years. This increase would have contributed to save €82,790 per 1,000 screened patients in 6 months of treatment. In this cohort, HLA-B*5701 test would have supposed a cost of €17,893 achieving savings of €64,897.

CONCLUSIONS: The systematic HLA-B*5701 genotyping supposes an additional cost of €334 per SHSR avoided. Regarding antiretroviral treatment costs, HLA-B*5701 test supposes less cost than the savings of the greater ABC prescription with the advantage that the incidence of SHSR decreases from 5 to 0.2%.

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Cod: 1363

DEVELOPMENT OF A PHARMACOGENETIC-BASED ACENOCOUMAROL DOSING ALGORITHM FOR BULGARIAN PATIENTS WITH CARDIOVASCULAR DISEASES

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BACKGROUND: Acenocoumarol is an antagonist of vitamin K, which is used in anticoagulation therapy mainly in Central Europe and Latin America, as well as in Bulgaria. The therapy with this medicine shows large interindividual and interethnic dose variability.

METHODS: The aim of our study was to developed a pharmacogenetic acenocoumarol dosing algorithm in 119 Bulgarian patients (derivated cohort) on stable anticoagulant therapy. Before developing the mathematical model we investigated the effect of genetic and non-genetic factors on acenocoumarol dosage by multiple linear regression analysis for derivated cohort of patients. The algorithm based on the obtained data was established and validated in testing cohort from 50 unrelated patients. All patients were genotyped for CYP2C9*2, CYP2C9*3 and VKORC1 -1639 G>A by High Resolution Melting assay. All observed polymorphic variants were confirmed by direct sequencing by Sanger.

RESULTS: It was found that VKORC1-1639G>A (25.5%), age (13.6%), CYP2C9*2 (7.8%), CYP2C9*3 (6.1%) and diagnosis (6.0%) significantly affected acenocoumarol dose variability in the studied Bulgarian patients from the derivated cohort. Taken together, these factors with additional factors such as gender (0.1%), weight (2.6%) and amiodarone use (3.0%) accounted for 46.5% of the acenocoumarol dose variability for pharmacogenetic model of dose prediction in Bulgarian population.

CONCLUSIONS: In this study we developed and validated pharmacogenetic algorithm for prediction of the required acenocoumarol dose for Bulgarian patients. The algorithms, based on three polymorphisms in VKORC1 and CYP2C9 genes, age, weight, type of diagnosis and gender could be readily applied in clinical practice for patients undergoing therapy with acenocoumarol.