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Short communication

The role of drug metabolizing enzymes in personalized therapy

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Introduction

Individual differences in drug response, both beneficial and adverse, has long been recognized as complex and common problem in clinical practice (Ramamoorthy et al., 2015). Pharmacogenetics (PGx) aims at identifying genes and genetic variants that affect the clinical outcome of therapy, i.e. determination of inherited genetic differences and genetic mechanisms that condition or disposition efficacy and toxicity of drugs (Jones 2013). PGx prediction of the therapeutic outcome in each patient individually, is a challenge and it's usage in clinical practice is still far from reality. The extensive research efforts undertaken over the past decade have identified several genetic markers that are strongly associated with outcomes of interest. Appraising the drug related function of CYP450 (CYP2D6, CYP2C9, CYP2C19, CYP3A5 and AKR1D1) genetic variants is the core for efficient modeling of population specific, cost-effective, PGx platform for individualization of drug therapy (Cabaleiro et al., 2015; Holmes et al., 2011; Jiang et al., 2015; Kapedanovska Nestorovska et al., 2014; López-Rodríguez et al., 2008; Patel et al., 2014; Rejon-Parrilla et al., 2014) .

The objective of this study is to determine the differential expression of polymorphic CYP450 genes and the correlation of mRNA levels in the liver and peripheral blood, to evaluate the clinical validity of the CYP450 phenotype in prediction of pharmacokinetic properties and therapeutic outcome of substrate drugs (CYP2D6 for risperidone, CYP2C19 for clopidogrel and CYP2C9 for ibuprofen) and to assess cost-effectiveness of PGx platform for individualized treatment with risperidone and clopidogrel in our country.

Materials and methods

The studies included a total of 482 subjects, of which 230 healthy volunteers and 252 patients. The presence of single nucleotide polymorphisms is determined by using the Real-Time Polymerase Chain Reaction while the relative mRNA level of the CYP2D6, CYP2C19, CYP2C9, CYP3A5 and AKR1D1 genes, in the liver and peripheral blood, was determined by the method of qRT-PCR. Plasma and urinary concentrations of risperidone and 9-OH risperidon as well as of ibuprofen in healthy volunteers and patients with psychiatric disorders are determined using a validated HPLC-MS / MS and HPLC. Decision tree model, including only direct drug related costs was used to evaluate the economic viability of the PGx application in individualization of Rispiridone and Clopidrogel therapy in our country.

Results and discussion

According to the results, the relative CYP450 mRNA levels and the degree of their mutual correlation in liver and peripheral blood indicate tissue specific, sexually dimorphic, cis /trans regulated gene expression and activity. The CYP3A5 gene expression in blood can be used as a biomarker to study the physiological and pathological variations of CYP2D6, CYP2C9, CYP2C19 and AKR1D1 enzymes. Association of CYP450 allele variants with drug pharmacokinetics and treatment outcome, (CYP2D6 for risperidone, CYP2C9 for ibuprofen and CYP2C19 for clopidogrel), confirm the genetic basis of variability in drug response in patients from R. Macedonia. Risperidone metabolic ratio is a useful therapeutic biomarker to recommend CYP2D6 genetic testing to guide the present or future treatment of patients.The PGx defined Risperidone dose strategy (assuming 99% test accuracy) was associ-

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ated with €7.6 /month/patient increase in total treatment cost and health gain of 0,11 QALY, yielding an ICER of €69.32/ QALY, compared to the traditional approach. Reduced PGx test accuracy (95% and 50%) augmented the ICER (€610.73/QALY and €2300.22/QALY, respectively), due to the €30.53/ month increase in the treatment for each incorrect genotyped patient. Total accumulated cost per patient for the PGx guided clopidogrel therapy was €99.049 versus € 107.62 for the traditional treatment strategy while the mean drug-associated cost was e €21.09 and €9.68, respectively. The cost associated with and due to side events hospitalization was 1.5-fold less in PGx compared to the traditional treatment. Economic assessment of genetic screening testing for mutations that affect the level of expression and functional activity of CYP2D6 and CYP2C19 genes justifies the application of PGx individualized treatment with risperidone and clopidogrel in our country.

Conclusion

The established association between the examined genetic variations, drug pharmacokinetics, clinically significant patient outcomes as well as the obtained pharmacoeconomic evidence, highlighte the opportunities of implementing PGx guided drug treatment in R. Macedonia.

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