Integrating Pharmacogenomics with Pharmacovigilance – Croatian experience

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For public health
Introduction

Pharmacogenomics is the study of variations of DNA and RNA related to drug response.

Integrating pharmacogenomics with pharmacovigilance (PhV) has a substantial role in searching post-marketing adverse drug reactions (ADR) and in drug development.
Aim of the study

To study the possible genetic associations with ADRs, as part of its pharmacovigilance program, the Croatian Agency for Medicinal Products & Medical Devices (HALMED) conducts a project in collaboration with the University Hospital Zagreb to collect DNA and phenotype data of ADRs cases using the international standardized phenotypic criteria.
Method

- Besides the data from spontaneous adverse reaction reporting system, the clinical data routinely recorded in hospital settings provide additional opportunities for identifying and quantifying ADRs.

- Since 2010 we have asked reporters of some ADRs to invite patients to participate in the study. Patients who agreed to participate signed an informed consent form were included.
Method

We established a Biological Sample Repository in the University Hospital Centre Zagreb, Lab for pharmacogenomics - accredited according to ISO 15189

We undertake genotyping to:

- identify novel associations or
- validate findings in cohorts of patients with well-defined phenotypes
Reports of ADRs

Analysis – assessment of the results

Individualization of therapy
## Connection between National ADR database and pharmacogenomics data

<table>
<thead>
<tr>
<th>ID prijave</th>
<th>Lijek pod sumnjom</th>
<th>Rosuvastatin</th>
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<th>Hepatic lesion</th>
<th>CYP2C9</th>
<th>DPYD</th>
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</table>

**Notes:**
- *2*<sup>2</sup> indicates a second-degree interaction.
- *1*<sup>1</sup> indicates a first-degree interaction.
DNA samples from patients with ADRs that have been collected and genotyped (examples)

<table>
<thead>
<tr>
<th>Drug</th>
<th>ADR</th>
<th>Pharmacogenetic marker</th>
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<td>statins</td>
<td>myotoxicity, hepatotoxicity</td>
<td>CYP2C9, CYP2C19, CYP3A4, SLCO1B1, ABCB1, ABCG2</td>
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<tr>
<td>warfarin</td>
<td>bleeding</td>
<td>CYP2C9, VKORC1, MDR1</td>
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<tr>
<td>clopidogrel</td>
<td>bleeding, ineffectiveness</td>
<td>CYP2C19, CYP3A4, ABCB1</td>
</tr>
<tr>
<td>dabigatran, rivaroxaban</td>
<td>bleeding</td>
<td>CYP3A4, ABCB1</td>
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CYP2C9 and ABCG2 polymorphisms as risk factors for developing adverse drug reactions in renal transplant patients taking fluvastatin: a case–control study

Aim: To investigate whether an association exists between fluvastatin-induced adverse drug reactions (ADRs) and polymorphisms in genes encoding the metabolizing enzyme CYP2C9 and the drug transporter ABCG2 in renal transplant recipients (RTRs). Materials & methods: Fifty-two RTRs that experienced fluvastatin ADRs and 52 controls matched for age, gender, dose of fluvastatin and immunosuppressive use were enrolled in the study. Genotyping for CYP2C9*2, *3 and ABCG2 421C>A variants was performed by real-time PCR. Results: CYP2C9 homozygous and heterozygous mutant allele (*2 or *3) carriers had 2.5-times greater odds of developing adverse effects ($\chi^2 = 4.370$; degrees of freedom = 1; $p = 0.037$; $\varphi = 0.21$, odds ratio [OR]: 2.44; 95% CI: 1.05–5.71). Patients who were the carriers of at least one mutant CYP2C9 allele (*2 or *3) and who were receiving CYP2C9 inhibitors, had more than six-times greater odds of having adverse effects than those without the inhibitor included in their therapy ($p = 0.027$; OR: 6.59; 95% CI: 1.24–35.08). Patients with ABCG2 421CA or AA (taken together) had almost four-times greater odds of developing adverse effects than those with ABCG2 421CC genotype ($\chi^2 = 6.190$; degrees of freedom = 1; $p = 0.013$; $\varphi = 0.24$, OR: 3.81; 95% CI: 1.27–11.45). Patients with A allele had 2.75-times (95% CI: 1.02–7.40) greater odds of developing adverse effects than those with C allele. Conclusion: Our preliminary data demonstrate an association between fluvastatin-induced ADRs in RTRs and genetic variants in the CYP2C9 and ABCG2 genes.
Preliminary Communication

ABCG2 gene polymorphisms as risk factors for atorvastatin adverse reactions: a case-control study

Aim: To explore the association between dose-related adverse drug reactions (ADRs) of atorvastatin and polymorphisms of ABCG2, taking into account the influence of CYP3A4 and SLC18B1 genes. Materials & methods: Sixty patients who experienced atorvastatin dose-related ADRs and 90 matched patients without ADRs were enrolled in the study. Genotyping for ABCG2 421C > A, CYP3A4*22, SLC18B1 388A > G, SLC18B1 521T > C variants was performed by real-time PCR. Results: Patients with ABCG2 421CA or AA genotypes had 2.9 times greater odds of developing atorvastatin dose-dependent ADRs (OR: 2.91; 95% CI: 1.22–6.95; p = 0.016) than those with ABCG2 421CC genotype. After adjustments for clinical and genetic risk factors, ABCG2 remained a statistically significant predictor of adverse drug reactions (OR: 2.75; 95% CI: 1.1–6.87; p = 0.03). Also, carriers of SLC18B1 521 TC or CC genotypes had 2.3 greater odds (OR: 1.03–4.36; 95% CI: 1.03–4.36; p = 0.043) of experiencing ADRs caused by atorvastatin in comparison with carriers of SLC18B1 521 TT genotype. Conclusion: Our study demonstrated an association between atorvastatin-induced ADRs and genetic variants in the ABCG2 gene.

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ABCG2 gene polymorphism as risk factors for atorvastatin ADRs: a case control study

Aim of the study:

- To explore the association between dose-related ADRs of atorvastatin and polymorphisms of ABCG2, taking into account the influence of CYP3A4 and SLCO1B1 genes and clinical risk factors.
Methods

Case-control study

- 60 patients who experienced atorvastatin-related myotoxicity or hepatotoxicity vs. 90 matched patients without ADRs

- data regarding age, sex, atorvastatin dose, concomitant drugs, comorbidities

- data regarding risk factors for atorvastatin ADRs (hepatic or renal dysfunction, perioperative periods, multisystem diseases, small body size and untreated hypothyroidism)
Methods

Genotyping by real-time PCR, TaqMan® DME Assays

*ABCG2 421 C>A (rs2231142)*

*CYP3A4*22 (rs35599367)*

*SLCO1B1 388 A>G (rs2306283)*

*SLCO1B1 521 T>C (rs4149056)*
Results

- Patients with ABCG2 421CA or AA genotypes had **2.9 times greater** odds of developing atorvastatin dose-dependent ADRs (OR: 2.91; 95% CI: 1.22–6.95; p = 0.016) than those with ABCG2 421CC genotype.

- After adjustments for clinical and genetic risk factors, **ABCG2 remained a statistically significant predictor of adverse drug reactions** (OR: 2.75; 95% CI: 1.1–6.87; p = 0.03;).
Conclusion

We have found that A allele carriers of ABCG2 421C>A (421CA and 421AA genotypes), responsible for reduced transport function, were at greater risk for developing dose related ADRs to atorvastatin, comparing to non carriers of this polymorphism.

This is the first study showing that variants of ABCG2 are predictor of atorvastatin ADRs!
PhV centres a valuable starting point for pharmacogenomic studies and may suggest investigations and subsequent individualized pharmacogenetic counselling after a reported ADR.
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