

Working towards the realization of personalized medicine - pharmacogenomic and etiological study of adverse drug reactions with severe cutan involvement, developing preventive systems and assays

OTKA 73296

## Background

The need to maintain the ability of people to act and participate dynamically and healthy in the everyday work and also in the family life is increasing and is closely bound with the development of new therapeutics and the optimalization of drug therapy.

The Dermatology Department of the Semmelweis University often sees patients with drug induced toxic or allergic skin diseases, and some of these patients present with very severe symptoms - each year one or two patients face the possibility of a lethal outcome. We were able to identify the clinically different forms of drug induced skin diseases by histology, medical history and by in vitro testing, because we have a good clinical team who is able to identify to all probability an infective skin rash, or complex, drug-infection interactions- or multiplex drug interactions and to differentiate them from the single drug induced side effects.

We have collected blood and skin samples from diseased patients with clinically different forms of drug induced skin diseases proven by histology, medical history and by in vitro testing. Furthermore, we extracted DNA from them and used them for the present study. We were able to perform in vitro testing by the drugs (lymphocyte transformation test) if the patient agreed.

We collected clinical data from altogether 80 patients and controls, 40 out of them who had taken lamotrigine or carbamazepine without adverse events and 40 who had taken one of these two drugs and had been treated for severe cutaneous drug induced adverse effects, including toxic epidermal necrolysis, severe erythema multiforme or severe maculopapulous rash.

From all the patients DNA samples were collected and analyzed for CYP2D6 and CYP2C19 polymorphisms and this work was initiated by an Amplichip CYP450 IVD kit on an Affymetrix Gene Chip Fluidics Station 450 equipment. One of the studies indicated a quality problem and the negotiations with the Roche representative, who activated and controlled the system in our laboratory led to the conclusion to send the data files to the international center. Analysis of the data files indicated that the Affymetrix Fluidics Station in our laboratory was operated by an old softver. The Affymetrix changed the whole softver system to a new Affymetrix Gene Chip Operating Software. This change needed also further changes to installation of the new 7G reading chips. The service, however, indicated further ongoing problems including the block of one working station. That problem could not been repaired therefore only three modules out of the four Fluidics Station are working currently, although

all the reading software in the Roche Amplichip CYP450 were reinstalled by the Hungarian representative of Roche.

To test the new Roche system we asked for two test chips which arrived by expired codes as recognized by the new IVD system. Due to these problems the whole CYP2D6 and CYP2C19 diagnostic system could be reinstalled as working recently.

DNA studies for lamotrigin sensitivity were performed by an Affymetrix Drug Metabolizing Enzymes and Transporters (DMET Plus Solution) chip. Preliminary genetic studies were performed by an Affymetrix Genotyping Console software on a DMET chip and relevant genes and polymorphisms are currently under re-testing. We also introduced the PCR analysis of some of these genes. Although within the extended investigation period we performed several genetic analysis including GSTM1 copy numbers, UGT1A1-4 polymorphisms, and we have to close the official studies now.

#### Further studies

Meanwhile we also studied and published individual cases with dermatological drug side effects.

Eosinophil fasciitis in a young previously healthy male who regularly used anabolic steroids and levo-tryptophan rich diet from uncontrolled animal sources we suspected as described previously the drug intake, and interestingly we confirmed a mycoplasma arginini infection possibly from animal origin. We also found a correlation between mycoplasma infections and severe drug side effects by PCR testings.

Under the OTKA period we also introduced the patch testing for drug sensitivity and submitted a paper on provement of metamizol-induced multiple drug eruption.

We also screened a hungarian nuclear power plant for cutaneous malignancies and also wanted to exclude or confirm the role the UV induced cutaneous tumors among the workers and also asked for drugs inducing photosensitivity but none of the three identified tumor patients was the drug intake was relevant, but the OTKA citation is there.

One LTT (lymphocyte transformation test) investigation summary and one clinical erythema multiforme study was published from the collected data base of the Clinic.

Special remark. Considering the fact, that some pharmacogenomic investigations are still ongoing, we would like to ask for another evaluation in 6 months.