Stevens-Johnson Syndrome, toxic epidermal necrolysis (SJS/TEN), DRESS (drug reaction with eosinophilia and systemic symptoms), and acute generalized exanthematous pustulosis (AGEP).
Objective: To identify serious cases of (CADR) and the main suspected drugs.
Materials and Methods: Retrospective observational, between 2008 and 2014 at the Clinical Pharmacology Service of Hospital Universitario de la Princesa (Madrid) have identified 28 cases of severe skin reactions induced by drugs.
Results: Twenty-eight (CADR), 18 women and 10 men, mean age 43.1 years, (35.7%) in dermatology services, UCI, internal medicine. The main identified toxicodermia was AGEP (35.71%), followed by DRESS syndrome and SJS / TEN (25%), erythema multiforme (7.14%), leukocytoclastic vasculitis and linear IgA bullous dermatitis (3.57%). Main identified drug was phenytoin (28.75%), followed by amoxicillin/clavulanate (14.28%), carbapenems, antiretroviral treatment, piperacillin/tazobactam and magnesium metamizol (7.14%), and allopurinol, tramadol, NSAIDs, vancomycin, clindamycin, ranitidine, and simvastatin a (3.57%). Mortality rate was: 28.57% (n = 8), of which 4 by SJS/TEN, 2 by DRESS, and 2 by AGEP total of 8 patients.
Conclusions: Serious toxicodermies in the Hospital de la Princesa have a low frequency but are associated with high mortality, risk of complications and sequelae; Very similar to that found in other studies, the most frequent is acute generalized exanthematous pustulosis.

TARGETED EXOME RESEQUENCING: ADME PHARMACOGENETICS IN HUMAN LIVER

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High-throughput approaches including Next-Generation Sequencing (NGS) offer the opportunity to analyze a large number of genes to detect known and novel single nucleotide variants (SNVs) and copy number variations (CNVs). We have developed a panel-based targeted NGS pipeline for comprehensive sequence analysis of 341 genes involved in absorption, distribution, metabolism and excretion (ADME) of xenobiotics and endogenous substances.

DNA enrichment for NGS was specifically designed for optimal capturing of all exonic, exon/intron boundaries, 5' and 3'UTRs of the selected target genes with a total target size of 1.17 Mbases. A set of 150 extensively characterized Caucasian liver samples was analyzed. Variants were compared to available SNV data in databases (dbSNP, DGV). Validation was performed using Illumina HumanHAP300 SNP arrays and other genotyping methods. The impact of SNVs/CNVs on gene expression (Illumina Human WG6v2) was assessed.

Resequencing revealed more than 2 GB mappable reads containing about 29,500 variant positions with a mean coverage of about 140-fold. About 40% of observed SNVs were not yet listed in dbSNP database and one third of them were rare in our sample collection. Association analysis of SNVs with expression data was performed gene family-wise. For example, within 11 genes of human CYP families 1, 2 and 3, a total of 3 CNVs and 226 SNVs could be detected. Of these, 18 were not listed in dbSNP database, including ten missense mutations found as single observations. Their functional prediction (SIFT/PolyPhen) revealed deleterious effect for CYP1A1 (R98W, H60L), CYP2C8 (R124W, L268Q), CYP2C9 (S115R, Q324*), and CYP2E1 (I383M). Association analysis of SNVs/CNVs with expression data will be presented.

Our targeted NGS approach on an ADME gene panel with its custom bioinformatics pipeline is a highly efficient and sensitive method for comprehensive pharmacogenomic studies. Moreover it provides high coverage to detect rare known and novel variations.

The study was supported by the German BMBF (VLN grant 0315755) and by the Robert Bosch Foundation, Stuttgart, Germany.

AGENTS ACTING ON RENIN-ANGIOTENSIN SYSTEM: THE IMPACT OF GENERICS AND PRICE TRENDS IN CROATIA

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Adequate cardiovascular therapy that includes usage of agents acting on renin-angiotensin system (RAS), (ATC, C09) results in the reduction of cardiovascular morbidity and mortality. It is important to establish measures for higher usage of cheaper generics which will lead to the reduction of the healthcare costs. The aim of our study was to identify and analyse changes in the usage of original and generics drugs in RAS subgroup agents in Croatia from 2000 to 2013 and to identify the rate of the generic drugs usage as well as the average price for 1 DDD.

Data on the consumption have been obtained from the database IMS (International Medical Statistics) for Croatia. According to the World Health Organization Collaborating Centre for Drugs Statistics Methodology annual volumes of drugs are presented in defined daily doses/1000 inhabitants/day (DDD/1000), while drug costs data are presented in Euro per DDD.

The usage of original drugs increased from 5.86 DDD/1000/day to 63.56 during the investigated period and generics increased from 52.70 to 136.32. Consumption share of generics decreased from 90% in 2000 to 56% in 2006, and then we had constant increase to 68% in 2013. Average price of 1 DDD for both original and generic drugs in C09 subgroup decreased in total from 0.31 EUR/DDD in 2000 to 0.16 EUR/DDD in 2013, which is decrease of 48.91% (39.42% for originals, and 55.57% for generics).

The national healthcare policy promoting generics resulted in their increase of usage up to 2013, but due to the introduction of new INNs in subgroup (Angiotensin II antagonists, plain and combinations) it was less obvious than expected. The price trend showed price decrease in originals and generics as a result of price reduction policy introduced by Croatian National Insurance Company, but it is necessary to introduce new measures for further generic promotion.

MICRO RNA-DEPENDENT REGULATION OF THE FARNESOID X RECEPTOR

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Background: The transcription factor farnesoid X receptor (FXR) plays an important role in the regulation of bile acid and lipid homeostasis and has the potential to enfold protective effects against different cancer forms, such as hepatocellular or colon carcinoma. The short non-coding microRNA miR-192 is, like FXR, mainly expressed in the liver and colon, plays a crucial role in the pathogenesis of colon carcinoma and serves as a reliable serum biomarker for