Conference Scene

Pharmacogenomics at the second PharmSciFair 2009: adverse drug reactions and clinical implementation

Second PharmSciFair 2009
Nice, France, 8–12 June 2009

From 8th to 12th June 2009, the second PharmSciFair took place in Nice, France. Sessions were organized on different types of pharmaceutical research. Two pharmacogenomics sessions were organized by the European Federation for Pharmaceutical Sciences Network on Research in Pharmacogenetics/Pharmacogenomics. The topics of the sessions were adverse drug reactions and clinical implementation. Important conclusions of the presentations were that there has been much progress in the field of pharmacogenomics and that implementation in clinical practice is not as easy as it was once thought. Large prospective trials might be necessary to prove clinical relevance.

Conference details

This Conference Scene provides an overview of the two pharmacogenomics sessions organized by the European Federation for Pharmaceutical Sciences (EUFPS) Network on Research in Pharmacogenetics/Pharmacogenomics at the second PharmSciFair, which was held at the Acropolis Convention Center in Nice, France on June 8–12, 2009. The sessions were focusing on the 'Pharmacogenomics of Adverse Drug Reactions' and on the 'Clinical Implementation of Pharmacogenomics.'

Pharmacogenomics of adverse drug reactions

The first part of the pharmacogenomics session, co-chaired by Ann Daly (Newcastle University, Newcastle-upon-Tyne, UK) and Anke Hilse Maitland-van der Zee (University of Utrecht, Utrecht, The Netherlands), gave an overview of the pharmacogenomics of adverse drug reactions. The first presentation was given by Patricia van den Bemt (University of Utrecht). She showed further evidence that adverse drug reactions are an important cause of hospitalizations. She performed a prospective, multicenter study and found that 5.6% of all acute hospital admissions were medication related. Almost half of these admissions appeared to be potentially preventable. The top three drugs involved in apparently nonpreventable Hospital Admissions Related to Medication (HARMs) [1] were anticancer drugs (23%), coumarin derivatives (14%) and acetylsalicylic acid (8%). These nonpreventable HARMs may become partly preventable in

the future by including pharmacogenetic information. Fiona Brew (Affymetrix, Wooburn Green, UK) presented 'Modern tools of genotyping drug-related SNPs: the DMET™ chip'. The DMET chip contains 1936 polymorphisms in 225 genes of drug metabolism and transport, as well as some receptors. Genotyping with the DMET chip takes, from start to finish, 48 h and, therefore, provides a faster discovery of genetic variations if compared with conventional methods and seems to be a suitable tool particularly in larger clinical studies. Ann Daly linked liver injury caused by commonly prescribed drugs to a genetic basis. Drug-induced liver injury (DILI) is a rare but serious toxicity. To find genes that might be related to DILI she performed the DILIGEN study, which is a multicenter study across the UK focusing on co-amoxiclav and flucloxacillin and seeks to identify genetic determinants of DILI. This case-control study showed that a major determinant of DILI is the genotype of HLA for co-amoxiclav and flucloxacillin, more specifically *HLA-DRB1*1501* and *HLA-B*5701*, respectively [2]. Iztok Grabnar (University of Ljubljana, Ljubljana, Slovenia) led a short presentation on the influence of the *CYP2D6* genotype on the pharmacokinetics of risperidone in patients with schizophrenia. As the active moiety arises from hydroxylation of risperidone by *CYP2D6* and *CYP3A4*, the *CYP2D6* genotype might be an important predictor for the steady-state plasma concentration of the risperidone active moiety and clinical outcome. In the second short presentation Anke Hilse Maitland-van der Zee presented

**Rianne MF van Schie¹,
Ingolf Cascorbi² &
Anke Hilse Maitland-van der Zee^{1*}**
**for the European Research
Network on Pharmacogenetics/
Pharmacogenomics**

^{*}Author for correspondence:

¹Utrecht Institute for Pharmaceutical Sciences, Division of Pharmacoepidemiology and Pharmacotherapy, Sorbonnelaan 16, PO Box 80082, 3508 TB Utrecht, The Netherlands

Tel.: +31 302 534 042;

Fax: +31 302 539 166;

a.h.maitland@uu.nl

²University Hospital Schleswig-Holstein, Institute of Experimental and Clinical Pharmacology, Kiel, Germany

the study design of the Pharmacogenomics of Asthma in Children: Medication with Anti-inflammatory effects (PACMAN) Cohort Study. Approximately 10–15% of the children did not respond to the inhaled corticosteroids asthma treatment. In the PACMAN study, the effects of genetic variation on treatment response will be studied in children using inhaled corticosteroids therapy [3].

Clinical implementation of pharmacogenomics

The second part of the pharmacogenomics session focused on the clinical implementation of pharmacogenomics and was co-chaired by Ingolf Cascorbi (University of Kiel, Kiel, Germany) and Jan Raaijmakers (GlaxoSmithKlein, Zeist, The Netherlands). The first presentation of this session was about the challenges and limitations of translating pharmacogenetics into clinical practice presented by the co-chair Ingolf Cascorbi. Pharmacogenetic diagnostics are developed to predict clinical response to a drug and to explain adverse drug reactions. Dr Cascorbi exemplified drugs targeted to overexpressed or mutated proteins improving significantly the clinical outcome of tumor therapies or being subject of polymorphic metabolism in various disease fields that might become subject to pharmacogenetic dosing. However, implementation of pharmacogenetics for many drugs is not yet achievable due to a lack of large prospective studies. Moreover, implementation of pharmacogenetics may take place only for drugs with a small therapeutic window and long-lasting therapy. Examples of pharmacogenetic interactions that fulfill these criteria are coumarin derivatives on which Yoseph Caraco (Hadassah University Hospital, Jerusalem, Israel) and Rianne van Schie (University of Utrecht) focused during their presentations. Yoseph Caraco presented a first proof of genetically based therapy with warfarin. Polymorphisms in genes encoding CYP2C9, the metabolizing enzyme, and the target enzyme VKORC1 are major factors contributing to variability. To calculate an algorithm of a warfarin loading dose, healthy volunteers were exposed to a single warfarin dose in the Warfarin Sensitivity Index During Induction (WSIDI)-cohort. The algorithm considering physiological factors and the

genotypes of *CYP2C9* and *VKORC1* was then applied in patients with atrial fibrillation, leading to significantly faster stabilization of international normalized ratio. He concluded that using the pharmacogenetic data in the dosing is feasible. Rianne van Schie gave a short presentation on the study design of European Pharmacogenomics Approach to Coumarin Therapy; the first large-scale randomized controlled trial of a pharmacogenomic strategy for coumarin derivative treatment in Europe. This multicenter study will investigate the added value of genotyping before the start of anticoagulation therapy with warfarin, acenocoumarol and phenprocoumon, of which the last two mentioned are predominantly prescribed in continental Europe. Matthias Schwab (Margarete Fischer-Bosch Institute of Clinical Pharmacology, Stuttgart, Germany) gave an overview of the improvement of leukemia treatment. Acute lymphoblastic leukemia now has a much higher cure rate compared with several years ago. This success is a result of insight into clinical, immunological and genetic characteristics. Polymorphisms in genes encoding TPMT, the metabolizing enzyme of 6-mercaptopurine, the drug used to treat acute lymphoblastic leukemia, resulted in changes in drug response, though this knowledge is not yet implemented in clinical practice. Finally, Jan Raaijmakers explained the view of the pharmaceutical industry in his presentation. Sometimes, it has been said that the pharmaceutical industry has no interest in pharmacogenetics and individualized medicines because the market may become smaller and, therefore, the revenues of the companies will also be lower. Fortunately, Jan Raaijmakers pointed out in his presentation that the pharmaceutical industry also sees a lot of opportunities by implementing the genetic information of the patient in the treatment. Some medicines that did not reach the market in the past might have reached the market if they were only prescribed to patients with a certain genetic profile.

Conclusion

Although there are many nongenetic factors that play a role in lack of drug efficacy or the development of adverse drug reactions, it has been shown that pharmacogenomics

contributes significantly. In this pharmacogenomics session, it was shown that much progress has been made in the field. Pharmacogenomics will play a role in the future both in predicting efficacy of drugs and in predicting or explaining adverse drug reactions. Some large prospective randomized controlled trials have been already launched to prove the clinical benefit of inclusion of pharmacogenomic information into drug prescription and to translate pharmacogenomic findings into clinical practice.

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