**Pharmacokinetics and pharmacogenetics for a comprehensive approach to pharmacovigilance: critiques and ways forwards**

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Although randomized controlled trials (RCTs) are still considered the gold standard for the clinical research as a source of evidence based data, they have several limitations. Specifically, the limited duration as well as the limited number of patients, and the highly controlled setting don't allow to obtain real information on any drug safety and efficacy profile. Indeed, in a real world setting unexpected and/or rare adverse drug reactions (ADR) as well as drug-drug interaction (DDI) are frequently observed. Based on these limitation, pharmacovigilance (PV) is the discipline directed to the early identification of any suspicions of drug-induced expected/unexpected ADR in order to quantify any risk, which must be reported, signaled and evaluated. The main aim of pharmacovigilance is, therefore to understand and prevent any drug-related problem.

Among the different mechanisms which underlie drug-response, genetic factors could be involved in determining both ADR and clinical outcomes. In particular, pharmacogenetics is the area of research focused on the discovery of genetic variants which could influence drug response, and then can be used to identify patients with an increased risk of experiencing an ADR. The terms pharmacogenomics and pharmacogenetics are often used interchangeably. Pharmacogenomics refers to the simultaneous study of many genes that may affect drug response, while pharmacogenetics refers to research focused on a few specific genetic variants. Several biomarkers, which are significant pharmacogenetics molecular targets, could explained a priori inherited variants in genes involved in drug metabolism and/or transport that could to be important factors in determining inter-individual variability in drug response and leading to the risk of development unwanted ADR.

Based on the evidence derived from RCTs outcomes, the genotypization for different polymorphic genes could be able to support appropriate tailoring of pharmacological treatment for every patient, in terms of choice of the best medicine, dose and duration and, eventually, consideration of alternative treatments.

Indeed, in the last decade only small proportion of the pharmacogenetics tests have been integrated into the boxed warnings area of the Summary of Product Characteristics (SPC) of commonly prescribed drugs, such as warfarin, clopidogrel, abacavir and so on by regulatory agencies in USA and Europe.

The challenge remains to translate implementation of pharmacogenetics tests in clinical practice. The small numbers of studies lead to the absence of robust evidence demonstrating clinical utility and there are scant availability of clinical guidelines that may impact overall use of the tests.

In this scenario pharmacovigilance, through pharmacogenetics approaches, could guiding the clinicians to identify important factors determining inter-individual variability in drug response with a reduction of the population costs of drug-related morbidity.

Nowadays an emerging research area is represented by “pharmacogenovigilance” which could address unanswered questions combining expertise of both pharmacovigilance and genetic professionals.

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