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Editorial Open Access

New Approaches in Pharmacovigilance in the Pharmacogenomic Era: A Call for Papers

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Editorial

The presentation of the most recent developments in the field of drug safety falls very well within the scope of the Journal of Pharmacovigilance: pharmacogenetics is certainly one of these. It is the study of associations of genetic traits of individuals and their response to drugs and has become an important aspect to be considered both during drug development and in post-marketing surveillance not only to optimize drug efficacy, but also drug safety.

A global regulatory perspective on approaches to be followed through phases I to III of drug development was recently published by Maliepaard et al. [1]. These authors also examined the views expressed by regulatory agencies in documents published in the past decade. This aspect will not be covered here because, strictly speaking, it does not regard post-marketing pharmacovigilance.

Indeed, in this Journal, devoted to all aspects of pharmacovigilance, it is important to recognize that not all pharmacogenetic issues can be properly addressed before marketing authorization: as a matter of fact, in the past decade progress in knowledge of pharmacogenetic aspects has produced several examples of revision of the risk/benefit balance and, subsequently, of the approved label (or summary of the product characteristics) of marketed products. It has been estimated that approximately 15% of marketed products contain pharmacogenetic data in the label with a direct impact on patient treatment [2].

The first example is codeine, which is converted into morphine by CYP2D6: excessive prodrug activation, as it occurs in ultrarapid CYP2D6 metabolizers, may affect the safety to such a degree that standard doses of this agent may have fatal consequences [3, 4].

Other examples include clopidogrel and warfarin. Clopidogrel, used in cardiovascular prevention as an antiplatelet agent, is a prodrug metabolized mainly by CYP2C19 to its active metabolite. Poor CYP2C19 metabolizers and patient with reduced CYP2C19 function because of a drug interaction may have a higher rate of cardiovascular events: this aspect is still debated and is covered by a large literature [5].

The case of warfarin is even more complex [6]. It is a vitamin K antagonist inhibiting the C1 subunit of the vitamin K epoxide reductase (VKORC1) enzyme complex: the relevant gene may be affected by single nucleotide polymorphisms leading to variable warfarin dose requirements (this explains the so-called "warfarin resistance" and interethnic differences in dose requirements). In addition to polymorphisms affecting the VKORC1 gene, genetic polymorphisms in CYP2C9 also affect the pharmacokinetics of warfarin and contribute to variability in drug response.

In January 2014, the European Medicines Agency published a draft guideline [7] on key aspects for the use of pharmacogenomic methodologies in the pharmacovigilance evaluation of medicinal products. The guideline indicates the need for systematic inclusion of pharmacogenomic considerations in the Risk Management Plan for targeted therapies and provides requirements for post-authorization genomic data monitoring and collection. The document also calls for collaborative actions, such as consortium (biobanking)-based approach involving marketing authorization holders, academia and regulatory authorities.

Especially in the initial post-authorization period, genomic samples should be collected from every patient receiving a medication and experiencing a serious adverse drug reaction or lack of efficacy. New strategies are being developed to make this possible because neither drug companies nor academia can face this new scenario without a common effort. One example is the International Serious Adverse Event Consortium (iSAEC), a large scale private-public biomedical consortium, where biobanks are shared between stakeholders. Another example is provided by Wing et al. [8], who use serious drug-induced liver injury to illustrate how a database of routinely collected electronic health records can be used to facilitate rapid recruitment for genome-wide association studies. They propose an active monitoring model, where genetic sampling kits are sent directly to the physician of individuals identified as cases by continuous database surveillance. The clinician can directly obtain consent from the patient and take a blood sample to be sent to the study coordinator. This will enormously speed up research into this topic.

New strategies should also be followed when identifying new signals from pharmacovigilance: the traditional way of dealing with spontaneous reports of adverse drug reactions has inherent limitations [9], which can be partly overcome if the link to the original health record is maintained to allow free text search. In addition, the availability of easily accessible (both in terms of cost and technical feasibility) will certainly aid the development of approaches such as that proposed by Wing et al. [8]. Other consortia, such as the ARITMO consortium [10-11], have addressed the problem of drug-induced arrhythmias, which can be fully addressed only in the post-marketing phase because of the paucity of events (namely, *torsades de pointes*), which can become significant when drug exposure is high [12]. The pharmacogenetic aspects of drug-induced arrhythmias still deserve further research.

Hopefully, this Editorial will foster discussion on the revolution of pharmacovigilance in the pharmacogenetic era: the Journal can certainly provide a timely forum to exchange ideas on new ways of joining efforts to make post-marketing pharmacovigilance as efficient as possible after a signal has been generated through continuous

database surveillance. Now, it is up to the scientific community to accept this challenge and submit papers reporting innovative examples of how genetic testing can assist informed decisions and improve patients' safety.

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