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Opportunities and limitations: the value of pharmacogenetics in clinical practice

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There is wide discussion on the impact and benefit of pharmacogenetic biomarkers but also increasing evidence that the situation is much more complex than anticipated one or two decades ago. Modern pharmacogenomics/pharmacogenetics is related not only to germline genetic variation but to an entire range of molecular traits involved in pharmacokinetics and dynamics which may influence both drug efficacy and safety. This increasing and more complex knowledge requires new diagnostic technologies, new approaches to design of clinical studies combined with appropriate data analyses for the complex data likely to be generated and finally new approaches from international drug regulators. This themed issue aims to summarize the current state of the art of major clinical areas where pharmacogenetics play a substantial role, discusses fields where genetic traits still need to be considered more carefully, outlines modern approaches to data analysis and finally a change of regulatory decision making. The articles in the issue cover a range of areas including a description of an already implemented example of pharmacogenetic testing where some issues remain, reports on several examples where pharmacogenetic testing is possible but its benefit is still controversial and the areas of greatest complexity such as pharmacoepigenetics and systems pharmacology which are still far removed from clinical implementation.

The relevance of epigenetics, where gene expression can be modified in a tissue specific manner by processes such as DNA-methylation and histone acetylation, to drug response and toxicity is still poorly understood with far fewer studies on this aspect compared with genomic studies. Another form of epigenetic regulation involves microRNAs which regulate mRNA stability and protein translation processes. Since microRNAs are differentially expressed in diverse tissues and are themselves dependent from regulatory factors, microRNA interaction may contribute to varying gene expression. Progress on understanding the epigenetics of drug transporters has been made recently and this example is considered in detail by Haenisch *et al.* [1] in the current issue. In contrast to the drug metabolizing enzymes, the overall contribution of genetic variation to the function of drug transporters is poorly understood. Depending on the site of expression, the impact of genetics on expression and activity seems to vary and there are a number of studies showing contradictory results, at least in part. One explanation of such phenomena could be the influence of epigenetics. Similar pharmacoepigenetic studies on other genes relevant to drug disposition and response are needed but the progress made on transporters will serve as a useful paradigm.

Information obtained in clinical studies and in particular in daily clinical practice including genomic data or other omics technologies is becoming increasingly complex. Systems biology aims to develop mathematical methods to model networks, explaining the interaction, e.g. between genes and metabolic processes in complex diseases. In their excellent article, Hütt *et al.* give an insight into how systems biology tries to help to model genetic variation to finally allow a mechanistic understanding of these complex processes [2]. It is getting clearer that attempts to introduce personalized medicine into clinical practice may need inputs from systems biology.

Very recently, the European Medicines Agency (EMA) released a draft guidance on the use of

pharmacogenomics to improve safety monitoring of medicines for public discussion. The guidelines are intended to give a recommendation on how to assess pharmacovigilance issues associated with pharmacogenomics and how to translate the results into appropriate recommendations for the labelling of medicines. The guidelines were based in particular on established pharmacogenetic biomarkers having a clear association with drug efficacy or safety. This is further explained and discussed in the interesting article by Ehmann *et al*. from the EMA [3].

The views of regulators on clinical implementation of genetic testing in medicine are discussed in more depth from the perspective of North America. Lesko & Schmidt outline in their paper how personalized medicine became the major goal in the last two decades exemplifying the case of successful implementation of trastuzumab in the treatment of HER2-overexpressing breast cancer [4]. More recently, the regulatory authorities, especially in the US, have emphasised the importance of using information on germline and somatic mutations in clinical trials in order to guide the decision-making during drug development. Further attempts to foster submission of genomic data to the FDA and in particular to co-develop drugs accompanied by genetic testing tools did however not receive widely acceptance by the pharmaceutical industry. On the other side, substantial efforts have been made to update labels of previously approved drugs with genetic information in North-America.

The issue includes three separate articles of particular relevance to cardiovascular pharmacology, one relating to a common adverse drug reaction and two on specific drugs where pharmacogenetic factors appear relevant to response.

From the view point of drug safety, long QT syndromes are an important cause of withdrawal of drugs from the market. Cardiac arrhythmias including the most serious forms such as torsades de pointes are often fatal. Therefore pharmacovigilance pays particular attention to drugs potentially associated with long QT syndromes. Examples of such drugs include tricyclic antidepressants, antimicrobials such as the quinolones, some antipsychotics and methadone. Petropoulou *et al*. summarize current knowledge on genetics of pro-arrhythmic adverse drug reactions [5]. They report that more than 700 variants that are potential risk factors for toxicity have now been identified in at least thirteen genes which mainly code for potassium, sodium and calcium ion channels. The authors summarize that in the future clinicians may use genetic testing to identify prospectively subpopulations at elevated risk of cardiotoxicity.

The publication of two recent large clinical trials on genotype-guided dosing of the anticoagulant warfarin has generated considerable interest [6, 7]. The European EU-PACT study confirmed that the use of pharmacogenetics in individual dosing shortened the time needed to reach the therapeutic INR by 8 days and more subjects remained in the therapeutic window. Also safety features such as incidences of excessive anticoagulation having an INR ≥4.0 were improved in the genotype guided treatment group suggesting that indeed pharmacogenetics guided dosing may increase the safety and accuracy of warfarin therapy. In contrast a US-based study failed to show a significant improvement when genotype guided warfarin therapy was used. Two further study arms of the EU-PACT study investigated genotype guided dosing of the vitamin K antagonists phenprocoumon and acenocoumarol. Though overall there was also lack of a significant difference compared with conventional study arms for these two drugs, an advantage for genotyping was seen early in the anticoagulation process [8]. All three studies did not investigate long term data such as the avoidance of thromboembolic events. Verhoef *et al*. [9] reviewed the knowledge on the impact of CYP2C9 and VKORC1 genetics on coumarin anticoagulant PK/PD before the publication of the above mentioned NEJM papers. Their article gives a comprehensive overview of the large number of studies performed already in this field and about the quality of mathematical algorithms used to optimize individual dosing.

The platelet inhibitor clopidogrel is a pro-drug that requires enzymatic activation to be transformed to an active P2Y12-inhibitor. CYP2C19 makes an important contribution to this activation and CYP2C19 genotype was shown to be a strong predictor of platelet inhibitor activity, in some but not all studies. There is an ongong discussion in the field of cardiology on whether CYP2C19 genotyping may be useful for further stratification of antiplatelet therapy. Trenk & Hochholzer [10] review carefully the current data and concluded that the CYP2C19 genotype explains only 5–12% of the overall variability in ADP-induces platelet aggregation on clopidogrel. This dampens to some extent the initial enthusiasm raised after the first intriguing studies on the risk of stent rethrombosis and CYP2C19 genotype.

Since the early days of pharmacogenetics, psychiatry has been a clinical area that has been to the fore in terms of potential for clinical implementation. Since it is well known that antidepressant drugs, such as the tricyclic nortriptyline, are metabolized by the polymorphic cytochrome P450 enzyme CYP2D6, the question arose to what extent the interindividual differences in pharmacokinetics play a role on the risk of side effects or treatment failure. However, other classes of antidepressants having less side effects that also followed other metabolic pathways and had different pharmacodynamic profiles were introduced subsequently, making it necessary to consider additional genetic factors to CYP2D6. It has now became clear that genetic factors affecting the pharmacodynamics of psychotropic drugs are very complex [11]. In their review Reynolds *et al*. give a comprehensive overview about the current knowledge of pharmacogenomics in psychiatry

and how genetic variants in receptors and membrane transporters contribute to disease susceptibility and drug response [12].

Interestingly, the important polymorphic drug metabolizing enzyme CYP2D6 seems to play a role also in endogenous processes. In the article by Penas-Lledo & Llerena [13], the authors pointed out that CYP2D6 is related to human behaviour as it is involved in the metabolism of dopamine and serotonin together with other endogenous compounds. Currently findings from the various clinical studies are difficult to interpret due to different settings and scoring systems. The authors conclude however that many studies in healthy volunteers suggest that CYP2D6 poor metabolizers have a personality profile characterized by higher impulsivity and anxiety than that seen in CYP2D6 extensive metabolizers.

In line with this, genetic variation in the catecholamine O-methyltransferase (COMT) enzyme and dopamine receptors can affect cognitive function following the administration of dopamine agonists and antagonists, as proven by magnetic resonance imaging (MRI) studies. Viviani *et al*. reviewed the role of MRI to visualize response to medication in brain behaviour circuits *in vivo* in humans [14]. Although still a developing area, imaging techniques such as MRI are a highly interesting tool to gain insight into brain function. It can be expected that such techniques will be an additional tool to help to understand better the nature of pharmacogenetics in drug treatment of psychiatric diseases and in assessing the genetics of brain function.

Three articles are concerned with the areas of oncology and immunosuppression. An intensive discussion is currently ongoing on the role of CYP2D6 in tamoxifen treatment in post-menopausal women with early breast cancer. Based on the fact that tamoxifen is a pro-drug that is metabolized in two steps to the active moiety endoxifen, this question was investigated in several clinical studies showing a differential response dependent on the CYP2D6 genotype. Since not all studies confirmed these initial findings, a fierce discussion has been launched on the reasons for these discrepancies. Brauch & Schwab, being representatives of major studies in this field who also contributed to deeper insights into the mechanisms of tamoxifen activation, picked up this discussion and delivered a comprehensive overview on current knowledge [15].

The question whether testing the genotype or phenotype for thiopurine S-methyltransferase (TPMT) may be helpful when prescribing thiopurine drugs such as azathioprine is reviewed by Lennard [16]. It is well established that TPMT poor metabolizers are at increased risk of leukopenia and certain guidelines have been developed under which conditions TPMT testing should be performed, such as the 'Clinical Pharmacogenetics Implementation Consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing' [17]. The advantages and disadvantages of both genotyping and phenotyping are carefully reviewed. Interestingly, there is a close relationship between the genotype of TPMT and poor TMP activity. However the intermediate phenotype has a concordance of only 70–86% to the determined genotype. The authors finally conclude that since TPMT deficient patients will experience profound myelosuppression when treated with thiopurine drugs, it is still cost effective to perform pre-treatment TPMT testing routinely to identify these individuals alone.

A close relationship between polymorphic drug metabolizing enzymes and the pharmacokinetics of immunosuppressants has been shown to contribute to the explanation of interindividual differences of trough concentrations of TOR inhibitors such as tacrolimus prescribed to transplant patients to prevent organ rejection. In particular, CYP3A5, absent in 80% of the Caucasian population, was established to play a key role. The question whether pre-emptive genotyping could be beneficial to achieve more rapidly the desired trough concentrations and to avoid side effects or even rejection episodes is discussed in the article by Elens *et al*. [18]. This article also highlights the role of other polymorphic factors contributing to the disposition of immunosuppressants.

In conclusion, there are an increasing number of large scale studies investigating the impact of pharmacogenomics on clinical practice available. Only a few show evidence for improved outcomes by simple genotype-guided dosing. However where such evidence exists, introduction of testing into routine clinical practice is increasingly possible. Other studies have revealed that more complex information has to be considered, often requiring in depth understanding of mathematic modelling. With the exception of oncology, attempts to use complex molecular markers for prediction of drug efficacy and safety are currently still at the level of basic research or early clinical studies.

Competing Interests

There are no competing interests to declare.

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