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PHARMACOVIGILANCE

The contribution of pharmacogenetics to pharmacovigilance

Emmanuelle Bondon-Guitton [a,*], Fabien Despas [b], Laurent Becquemont [c]

[a] *Service de pharmacologie médicale et clinique, centre Midi-Pyrénées de pharmacovigilance, pharmacoépidémiologie et informations sur le médicament, pharmacopôle Midi-Pyrénées, faculté de médecine, université de Toulouse, CHU, 37, allées Jules-Guesde, 31000 Toulouse, France*

[b] *Service de pharmacologie médicale et clinique, faculté de médecine, université de Toulouse, CHU de Toulouse, 37, allées Jules-Guesde, 31000 Toulouse, France*

[c] *CEA DSV/iMETI, division d'immunovirologie, IDMIT, département de pharmacologie, centre d'immunologie des infections virales et des maladies auto-immunes, hôpital Bicêtre, faculté de médecine, université Paris Sud, Assistance publique—Hôpitaux de Paris, 94270 Le Kremlin-Bicêtre, France*

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HLA

Summary Since the beginning of this century, information on pharmacogenetics appears in the summary of product characteristics (SPC) of drugs. Pharmacogenetic tests particularly concern the enzymes involved in the metabolism of drugs, among which P450 cytochromes. Some patients known as poor metabolisers eliminate some drugs more slowly, causing overdoses and adverse drug reactions (ADRs). The best-known examples are AVK and VKORC1-CYP2C9 or clopidogrel and CYP2C19. In the USA, the tests are recommended before the introduction of these drugs to prevent the occurrence of ADRs. Other tests are also commonly performed to address the toxicity of certain anticancer drugs (DPYD-capecitabine, UGT1A1-irinotecan, TPMT 6-mercaptopurine). Pharmacogenetic testing is also available to identify HLA loci that are very strongly associated with the occurrence of immuno-allergic reactions to a specific drug. The best-known example is HLA-B*5701, strongly associated with hypersensitivity to abacavir, and this test is now always prescribed before the instatement of this drug.

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* Corresponding author. Service de pharmacologie médicale et clinique, faculté de médecine, 37, allées Jules-Guesde, 31000 Toulouse, France.

E-mail address: emmanuelle.bondon@univ-tlse3.fr (E. Bondon-Guitton).

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Abbreviations

5-FU	5-fluorouracil
ADP	adenosine diphosphate
ADRs	adverse drug reactions
AVK	antivitamin K
CYP2C9	cytochrome P450 2C9
CYP2C19	cytochrome P450 2C19
CYP2D6	cytochrome P450 2D6
CYP3A4	cytochrome P450 3A4
DPYD	dihydropyrimidine dehydrogenase
EGFR	epidermal growth factor receptor
FDA	Food and Drug Administration
FU-H2	dihydro-5-fluorouracil
HLA	human leucocyte antigen
INR	international normalized ratio
IWPC	International Warfarin Pharmacogenetics Consortium
KRAS	Kirsten Ras protein
SPC	summary of product characteristics
SN-38G	SN-38 glucuronide
TPMT	thiopurine methyltransferase
6-TGN	6-thioguanine nucleotides
UGT1A1	uridine diphosphate glucurunosyltransferase 1A1
VKORC1	vitamin K epoxide reductase

Introduction

Pharmacogenetics is the study of the influence of the physiological variability of our genome on response to medications. By identifying functional polymorphism on the genome, the aims are:

- to identify subjects who are non-responders to certain drugs or medications;
- to tailor dosage of certain drugs to each individual;
- to identify subjects who are at risk for developing adverse drug reactions (ADRs) [1].

To review the contributions of pharmacogenetics to pharmacovigilance we mainly focus on the third of these aims. Likewise, the subject of tumoral biomarkers (epidermal growth factor receptor [EGFR], B-RAF protein, KRAS protein (Kirsten Ras), etc. enabling the identification of responders in targeted therapies will not be broached here.

Finally, this overview will mainly focus on the enzymes involved in metabolising drugs, which, when they are deficient a result of deleterious genetic variants, lead to a drop in clearance rates for certain drugs, a lengthening of their half-life, and hence overdoses and ADRs.

The contributions of pharmacogenetics in oncology

Irinotecan and UGT1A1

Irinotecan is a topo-isomerase 1 inhibitor indicated in the treatment of advanced colon cancer. Uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) is involved in the metabolic de-activation of SN-38, the active metabolite of irinotecan, to form inactive SN-38 glucuronide (SN-38G). The *UGT1A1* gene is extremely polymorphous, which translates into highly variable metabolic potential depending on individuals. One of the specific variations of the *UGT1A1* gene involves polymorphism in the promoter region known as the variant UGT1A1*28. This variant and other congenital deficiencies in UGT1A1 expression (such as Crigler-Najjar disease and Gilbert's syndrome) are associated with reduced activity of this enzyme. Subjects who are homozygous for the UGT1A1*28 allele amount to around 15% of the Caucasian population. Data from a meta-analysis indicate that subjects who are homozygous for the UGT1A1*28 allele present a higher risk of haematological toxicity than heterozygous subjects or carriers of the two wild alleles [2]. In presence of the UGT1A1 genotype, the occurrence of diarrhoea following irinotecan administration has been observed, especially at high doses or in association with 5-fluorouracil. However, although these UGT1A1*28/*28 homozygous patients have an increased risk of serious ADRs, they also appear to have better outcome in terms of survival [3]. The pharmacogenetic test is as yet not compulsory in France, but among patients identified as homozygous for UGT1A1*28, enhanced surveillance is recommended to detect any haematological toxicity (Campto® SmPC).

Mercaptopurine and thiopurine methyltransferase TPMT

Mercaptopurine is an antimetabolite analogous to purines indicated in leukaemia. It is a pro-drug, and to reach cytotoxicity it needs to be converted by enzymes in the cell into active metabolites, thioguanine nucleotides or 6-TGN. Part of the mercaptopurine is also converted into other inactive metabolites by thiopurine methyltransferase (TPTM). When TPTM is not active or not very active, on account of the polymorphism of the gene, a greater quantity of 6-TGN is formed and the patient is exposed to an increased risk of neutropenia. From a phenotype viewpoint, there are slow metabolisers (0.3% of the population) and intermediate metabolisers (6—11% of the population) [4]. There is very good correlation between phenotype and genotype. Screening for TPMT activity deficit before treatment with 6-mercatopurine in adult leukaemia avoids serious neutropenia, potentially fatal for patients who are slow metabolisers. Depending on the scale of the deficit, and after risk-benefit assessment, treatment can be instated at a reduced dose, or else another drug can be proposed [5]. In heterozygous children, in case of acute lymphoblastic leukaemia consolidation, the initial dose should be maintained, with frequent neutrophil monitoring, because these patients have a better clinical response [6]. In France, this pharmacogenetic test is not compulsory, while it is recommended in the USA [7]. According to the SmPC for Xaluprine®: ''TPMT genotyping or phenotyping can be used to identify patients with absent or reduce activity. (...) The optimal starting dose for homozygous deficient patients has not been established.'' Measurement of intra-erythrocyte 6-TGN levels can also enable detection of a TPMT deficit.

5-fluorouracil, capecitabine, and dihydropyrimidine dehydrogenase

5-fluorouracil (5-FU) is an antipyrimidine in the antimetabolite class, and capecitabine, a 5-FU pro-drug, is a

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