Personalized anticoagulant therapy

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Following on from the completion of Human Genome Project in 2003 and through continuing advances in genome sequencing technology, scientists hope to be able to predict with exquisite precision, whether or not an individual is developing a disease now, will develop the disease in the future, will respond to treatment or have a serious reaction to a particular drug. Based on this information, physicians will be able to prescribe the right drug to the right patient at the right dosage in the framework of personalized or individualized medicine. As Brooke Byers of Kleiner Perkins Caufield and Byers states: "Personalized medicine is our chance to revolutionize health care, but it will require a team effort by innovators, entrepreneurs, regulators, payers, and policymakers". The emergence of pharmacogenomics-guided drug development has led to novel strategies in the management of patients with bleeding and thrombotic disorders, enabling a personalized approach in this area of medicine, which we discuss in this article.

Ancient beginnings for modern medicine

The concept of personalized medicine is not new and dates back to the time of Charaka Samhita (1500BC), who practiced Ayurveda, a natural health care that originated in India more than 5000 years ago. Charaka took the first step towards personalized medicine and said, "every individual is different from another and hence should be considered as a different entity. As many variations are there in the universe, all are seen in human beings". At the time when Hippocrates practised medicine, the established school of medicine was the Cnidian School (approximately 2500 years ago), which considered the body to be merely a collection of isolated parts and saw disease manifesting in a particular organ or body part as affecting that particular body part alone and not that the whole body was involved. Hippocrates (500BC) disagreed with this concept and said that the body functioned as one unified organism, or physis. He combined an assessment of the four humours – blood, phlegm, yellow bile and black bile – to determine the best course of treatment for each patient. Hippocrates expanded on this unifying theory to assert, "it is far more important to know what person has the disease than what disease the person has". Modern medicine has, in fact, provided us with the scientific proofs of such ancient beliefs, courtesy of the Human Genome Project which shifted research focus towards the function of genome, its regulations and how sequence variations could lead to disease and cause inter-individual variations in therapeutic response.

The term pharmacogenetics, first introduced by Vogel in 1959, is defined as the analysis of inherited factors that define an individual's response to drugs[2]. Definitions do differ slightly, but, in general, pharmacogenetics refers to the influence of a genetic variant on the response to a single drug, whereas pharmacogenomics is a broader term describing the study of how broader genomic changes or differences can affect drug efficacy and safety. Of particular importance was the discovery of the cytochrome P450 (CYP450) metabolic enzymes in 1977, which enabled our understanding of how these enzymes can alter drugs such that they could be easily eliminated from the blood circulation. This led us to realize that variations in these enzymes may influence the dosage of the drugs administered. It is astonishing to note that 5.3% of all hospital admissions are associated with adverse drug reactions[3] and many such reactions result from variations in genes that code for drug-metabolizing enzymes such as CYP450s[4,5]. These genetic variations are considered when dosing to avoid adverse effects. Panel-based tests to detect several variations in *CYP450* genes are now available. Variations in these genes are linked to the efficiency of metabolism of 25% of all drugs prescribed and therefore improved diagnostic testing has the potential to improve patient care for a large segment of the population[6]. Dosages of warfarin, a conventionally used oral anticoagulant drug and antiplatelet drugs such as aspirin and clopidogrel may be modified on the basis of the variations in *CYP450* genes and are perfect examples where personalized care may be initiated. For warfarin therapy, genetic variations in *CYP2C9* and vitamin K epoxide reductase (*VKORC1*), an enzyme

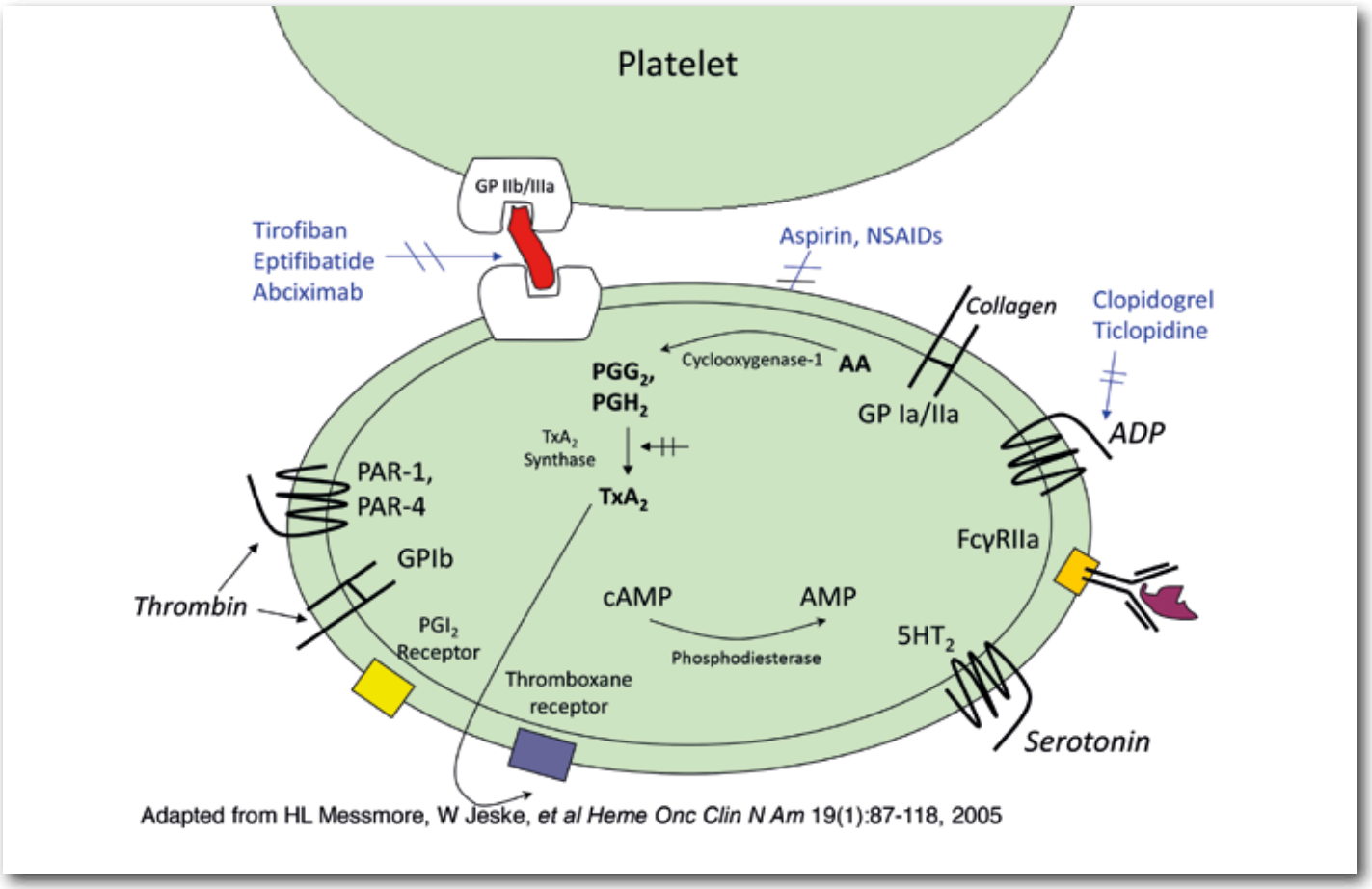

Figure 1. Figure reproduced with permission. **Platelet receptors**. The different platelet receptors and the sites of actions of various antiplatelet agents are shown. AA, arachidonic acid; GP, glycoprotein; $5HT_2$, 5-hydroxytryptamine receptor 2; NSAID, non-steroidal anti-inflammatory drug; PG, prostaglandin; TxA_2, thromboxane A_2.

that activates vitamin K, can result in either serious bleeding or thrombotic complications if the dosage is not tailored to the individual's requirements. The US Food and Drug Administration has now recommended genotyping for all patients before warfarin therapy.

Personalized anticoagulant therapy

The pharmacogenomics-based personalized practice of medicine is expected not only to reduce the number of adverse effects due to drug–drug interactions, but also to minimize drug failure or inter-individual variability in drug response, thereby curtailing healthcare expenditure. Genome-wide association studies are powerful tools to identify common single nucleotide polymorphisms (SNPs) associated with venous thromboembolism, the third leading cause of cardiovascular mortality. Variations in the hepatic microsomal enzyme CYP2C9 cause inter-individual differences in the plasma concentrations of drugs with a narrow therapeutic window such as warfarin. Furthermore, patients with variations in VKORC1, an enzyme inhibited by warfarin, may exhibit different sensitivities to the drug, warranting dosage adjustments or switching to new oral anticoagulant drugs such as dabigatran, rivaroxaban or apixaban, to prevent bleeding or thrombotic complications.

Platelets responsible for primary haemostasis play an integral role in cardiovascular atherothrombosis. Antiplatelet drugs such as aspirin, a cyclo-oxygenase 1 (COX-1) inhibitor, clopidogrel (an antagonist of the ADP P2Y12 receptor) and the glycoprotein IIb/IIIa receptor antagonists have a crucial therapeutic role (See Figure 1). Owing to the complex pathophysiology of atherothromboembolic complications and based on several triggers of platelet activation, there could be a significant incidence of residual arterial thrombosis in patients treated with currently available antiplatelet agents. Newer P2Y12 antagonists recently approved by the

United States Food and Drug Administration such as prasugrel, along with ticagrelor, cangrelor and elinogrel have significant advantages including more rapid, less variable and more complete inhibition of platelet function, over clopidogrel. There are several antiplatelet agents that are in advanced Phase 3 stages of clinical development which will determine whether these new P2Y12 antagonists or protease-activated receptor 1 (PAR1) antagonists will have more rapid and complete platelet inhibition with no bleeding risks or other side effects.

Drug–drug interactions with antiplatelet agents

A combination of aspirin and the P2Y12inhibitor clopidogrel has become a mainstay for the treatment of patients with acute coronary syndromes[7,8]. The pain associated with acute myocardial infarction is managed with morphine[7]. Clopidogrel, being a prodrug, requires metabolic activation by CYP450s in two steps[9]. Clopidogrel is effluxed via P-glycoprotein 1 or ATP-binding cassette subfamily B member 1 in the gut. After absorption about 90% is metabolized by esterase-1 to an inactive carboxylic acid derivative – SR26334 – whose concentrations are ~1000-fold higher than that of the active metabolite[10]. The two-step process of conversion of inactive into active metabolite involves the formation of an intermediate metabolite 2-oxo-clopidogrel and then conversion into an active R-130964 metabolite via cytochrome P450 enzymes such as CYP2C19 and CYP3A4, and, in a more minor fashion, CYP2B6, CYP1A2, CYP3A5 and CYP2C9[11]. The CYPC219*2 loss-of-function variant was recently reported to be associated with reduced antiplatelet response to clopidogrel and a 3-fold risk of stent thrombosis[12].

Genotyping for SNPs for the diagnosis of hereditary thrombophilia such as Factor V Leiden (G1691A) and prothrombin G20210A along with functional studies for determining Protein C, Protein S and antithrombin deficiencies is recommended for patients with a high risk of thrombotic disorders. Polymorphic genes including CYP450 isoforms such as CYP2C9, CYP3A4 or CYP3A5 and CYP2C19 and others are responsible for treatment failure of clopidogrel, a thienopyridine derivative, whose active form inhibits platelet $P2Y_{12}$ receptor normally activated by ADP. Genetic polymorphisms of haem oxygenase 1 (HO-1) and COX-1 have been associated with aspirin resistance in some Chinese populations. The Hemophilia Inhibitor Genetic Study has identified new genes such as *CD44*, *CSF1R*, *DOCK2*, *PAPK9* and *IQGAP2*, responsible for inhibitor development. Next-generation DNA sequencing will enable parallel sequencing of many genes at once for a defined panel of coagulation and bleeding.

Despite advancements in technology, the goals of personalized medicine to improve health and prevent disease are yet to be achieved[13-15]. The USA spends almost 80% of its unaffordable health care expenses on treating complex chronic diseases which are preventable. Healthcare costs for 25% of privately insured working-age people and 53% of privately insured people with low incomes are unaffordable, according to the Commonwealth Fund Health Care Affordability Index, a comprehensive measure of consumer health care costs.

President Barack Obama's Precision Medicine Initiative has highlighted renewed national focus on the ability of genomics and other emerging technologies to foster better understanding of the relationship between genetics, environment, lifestyle and the development of disease[16]. Genetic testing to target the dosing of warfarin is reported to result in 31% fewer hospitalizations overall for patients and up to 48% fewer hospitalizations for bleeding or thromboembolism[17]. The results of a prospective study in 3600 subjects indicated that hospitalization rates for heart patients were reduced by ~30% when genetic information was available to doctors prescribing the drug[17].

The future of personalized medicine in anticoagulant therapy is bright. The fields of genomics, transcriptomics, metabolomics and proteomics will have an impact on drug discovery. Tailored use of drug(s) based on an individual's unique genetic characteristics to achieve the maximum benefit and minimum side effects/complications will become the norm. ■

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