Case Study: Clopidogrel (Plavix®)

Key lessons learned
• Clinically significant differences in treatment response indicates a need for further investigation. • Differences may be attributable to metabolic or genetic variation. Genetic variation results from different forms (termed "alleles") of the same gene. • Allelic frequency differs between racial and ethnic populations. • Therefore, observed differences in treatment response between different racial or ethnic subgroups can, in some instances, indicate important genetic variants that may lead to important observations in drug discovery and development. • The importance of determining differences in treatment response or disease prevalence between patients in clinical trials is dependent on accurate and detailed demographic and clinical data collection.

Disease background

Blood clotting, the process of platelets clumping, is an important response to the control of bleeding, such as after cuts, injury, or surgery. Problematic blood clots, however, can also form within the blood stream and can cause serious health and cardiovascular events such as heart attack, stroke, difficulty breathing and other problems. People who have experienced a cardiovascular event are sometimes placed on medications to prevent blood clotting and those include anti-platelet therapy drugs.

Treatment for cardiovascular events has historically focused on aspirin therapy,[1] which reduces inflammation and helps block platelets from clotting. Additional therapeutic interventions beyond aspirin, especially for patients allergic or for those who are high risk for clotting, are sometimes needed. Clopidogrel, originally marketed under the trade name Plavix®, is a drug that inhibits platelet activation and aggregation and was initially approved in the U.S. in 1997 as a treatment for cardiovascular disease and atherosclerosis.

Discovery to genetic variation

The efficacy and safety of clopidogrel was investigated in clinical trials, leading to its emergence as an alternative therapy to aspirin, especially among individuals allergic to aspirin,[2] as well as in combination

[1] Angiolillo DJ, Bhatt DL, Gurbel PA, Jennings LK. Advances in antiplatelet therapy: agents in clinical development. The American journal of cardiology. 2009 Feb 2;103(3):40A-51A.

[2] CAPRIE Steering Committee. A randomized, blinded, trial of clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE). The Lancet. 1996 Nov 16;348(9038):1329-39.

therapy with aspirin.[3] Results from initial large-scale clinical trials suggested that clopidogrel, alone and also when combined with aspirin, reduced the occurrence of death, heart attacks, and stroke by 20% as compared to aspirin alone.[4] By 2010, clopidogrel was the world's second best-selling medicine – contributing $9.6 billion to the drug market.[5]

The mechanism by which clopidogrel works, however, was not discovered until after the drug was marketed; dosing was largely determined by clinical experience and changing therapeutic strategies.[5] Because of this, there were wide variances in drug response with a notable number of "non-responders." [5] While clinical utilization of clopidogrel was still being adjusted, biomolecular research on the difference in patient treatment responses also continued. Clopidogrel was discovered to be inactive until it is metabolized in the liver by proteins of the cytochrome P450 family, namely CYP2C19; this process results in the production of an active small molecule that then irreversibly blocks the P2Y12-receptor on platelets, a receptor that normally signals platelet activation and aggregation (i.e., clotting).[4] Any alteration, or genetic defect (e.g., loss-of-function [LOF]), in the availability or function of the liver protein CYP2C19 would reduce the conversion of clopidogrel to its active form and could explain "non-responders." These bio-mechanistic findings helped clarify the variability of treatment response to clopidogrel.

Further analysis of results from clopidogrel trials investigated populations with a genetic variation in CYP2C19 and discovered that the majority of individuals with LOF for CYP2C19 were from Asian regions.[6] In fact, studies in those of Asian descent (mainly Chinese, Japanese, and Korean) found LOF allele carriage may appear in more than 50% of individuals as compared to only 28% of Whites.[6] In addition, analysis of data relating to stent thrombosis outcomes indicated a difference in effect size of CYP2C19 LOF allele carriage between White (RR of 1.73) and Asian populations (RR of 4.88). [6] These are critical clinical findings since a reduced function of CYP2C19 results in a reduced response to clopidogrel and, therefore, an increased risk for a cardiovascular event. Genotyping individuals can aid in the development of therapeutic guidelines and will ultimately help clinicians and prescribers understand their patients' profiles and therapeutic response in advance of treatment.[7]

[3] Rezkalla SH, Benz M. Antiplatelet therapy from clinical trials to clinical practice. Clinical medicine & research. 2003 Apr 1;1(2):101-4.
[4] Angiolillo DJ, Bhatt DL, Gurbel PA, Jennings LK. Advances in antiplatelet therapy: agents in clinical development. The American journal of cardiology. 2009 Feb 2;103(3):40A-51A.
[5] Fitzgerald DJ, FitzGerald GA. Historical lessons in translational medicine: cyclooxygenase inhibition and P2Y12 antagonism. Circulation research. 2013 Jan 4;112(1):174-94.
[6] Sorich MJ, Rowland A, McKinnon RA, Wiese MD. CYP2C19 genotype has a greater effect on adverse cardiovascular outcomes following percutaneous coronary intervention and in Asian populations treated with clopidogrel: a meta- analysis. Circulation: cardiovascular genetics. 2014 Dec;7(6):895-902.
[7] Cresci S, Depta JP, Lenzini PA, Li AY, Lanfear DE, Province MA, Spertus JA, Bach RG. Cytochrome p450 gene variants, race, and mortality among clopidogrel-treated patients after acute myocardial infarction. Circulation: Cardiovascular Genetics. 2014 Jun;7(3):277-86.