Pharmacogenetics: where do we stand?

[1]**Anthony G Fenech** BPharm (Hons), PhD
[2]**Godfrey Grech** BSc, PhD

[1]Senior Lecturer, Department of Clinical Pharmacology and Therapeutics
University of Malta, Msida, Malta
Email: anthony.fenech@um.edu.mt

[2]Senior Lecturer, Department of Pathology
University of Malta, Msida, Malta
Email: godfrey.grech@um.edu.mt

Educational aims

- To emphasize the importance of genetic contributions to observed interpatient variablity in drug responses
- To discuss the practical applications of pharmacogenetic/pharmacogenomic knowledge
- To suggest how the introduction of pharmacogenetic tools may require additional skills from health care professionals
- To provide a basic picture of the roles being undertaken by FDA and EMA with respect to pharmacogenetics

Key words
Pharmacogenetics, pharmacogenomics, personalised medicine

"Our drugs do not work on most patients." Such did Allen Roses, then worldwide vice-president of genetics at GlaxoSmithKline, greet his audience, during a scientific meeting in London in 2003.[1] Nearly a decade has passed since then, and significant strides towards the development of genotype-guided prescribing have been made. Pharmacogenetics and pharmacogenomics are now an established area of pharmacology specialization, and they hold the promise of the key to personalized medicine, leading to safer and more effective patient-focussed therapeutic outcomes.

Introduction

Pharmacogenetics and pharmacogenomics, have often been hailed as the holy grail of therapeutics. Scientists have seen them as a major highway leading to personalized medicine, where the patient's most personal characteristic, his genetic profile, becomes a fingerprint which can be used to predict the way he will respond to a specific drug. Therapeutic outcome data collected from large clinical trials, may start to lose its meaning, unless those trials are also fortified with pharmacogenomic considerations. *Standardized dosing*, may give way to *genotype-predicted dosing*, perhaps reducing the need for clinically-based individual dose adjustments. Therapeutic drug monitoring data may be combined with genotype data, in order to enhance the maintenance of drug levels within the required therapeutic window. The benefit to risk ratio for most drugs may be improved, with consequently less adverse events, better therapeutic outcomes and improved pharmacoeconomic prospects.

Timeline

Science rapidly makes history. Watson and Crick published their cardinal paper describing the double-helical structure of DNA in 1953.[2] In 1957, Motulsky suggested that individual differences in drug efficacy and adverse effects might be due to inheritance.[3] Two years later, Vogel published his "Moderne problem der humangenetik"[4] wherein for the first time, the term "pharmacogenetics" was coined and used. This was followed by a landmark paper in 1968, where Vessel and Page showed similar drug pharmacokinetics in identical twins who share 100% of their genes as contrasted to fraternal twins who only share 50%.[5] This period even preceded the development of DNA sequencing technologies, which started to emerge in the 1970s. Scientific interest in the pharmacogenetic area gradually began to increase, and further landmarks were reported. However, it was only in the mid-1990s that a sudden escalation of peer-reviewed publications occurred, as evidenced by the National Centre for Biotechnology Information (NCBI)-maintained Pubmed database indices. During this period, the US-funded human genome project was underway, and interest in the functional relevance of DNA sequences was increasing in the scientific community. The completion and public availability of the human genome project data in April 2003, ushered us into

Table 1: Some important landmarks in the pharmacogenetics timeline

1953	James D Watson and Francis Crick published their paper on the double-helical structure of DNA.[2]
1957	Motulsky proposes that "inheritance might explain many individual differences in the efficacy of drugs and in the occurrence of adverse drug reactions."[3]
1959	The word "pharmacogenetics" appears for the first time in a paper published by Friedrich Vogel.[4]
1968	Vessel and Page show similar drug pharmacokinetics in identical twins who share 100% of their genes as contrasted to fraternal twins who only share 50%.[5]
1977	DNA sequencing technologies start to emerge.
1990	The human genome project (HGP) is initiated, and funded by the National Institutes of Health (USA) and other international partners. Projected project timeline is 15 years.[38]
2003	The HGP is completed, two years in advance of its original projected target date.[38]
2004	Roche AmpliChip Cytochrome P450 Genotyping test is given marketing clearance by FDA. This is the first pharmacogenetic test to be given FDA approval.[26]
2005	The European Medicines Agency (then known as EMEA, later known as EMA) establishes the Pharmacogenetics Working Party (PgWP). This later changed its name to the Pharmacogenomics Working Party, still maintaining the PgWP abbreviation.[32]
2005	The Food and Drug Administration (FDA) establishes the Interdisciplinary Pharmacogenomics Review Group (IPRG).[33]
2005	FDA gives marketing approval for The Invader UGT1A1 Molecular Assay. This is the first pharmacogenetic test to be approved by the FDA, following establishment of the IPRG.[28]
2009	Imperial College London announce their ongoing development of the SNP Dr pharmacogenotyping device.[37]
Today	Major pharmaceutical companies have incorporated pharmacogenomics into the drug discovery process,, published pharmacogenetic data is escalating exponentially, and translation from bench to bedside is well underway.

the post-genomic era. This has brought with it a torrent of new technologies, focussed on global analysis of whole genomes, rather than studies of individual genes. Genetics thus paved the way for genomics, and pharmacogenetics led to pharmacogenomics (Table 1).

What are pharmacogenetics and pharmacogenomics?

The Merck Manual[6] lists 26 different factors which can influence drug response in humans. These include well known variables such as age, gender, body weight, liver and kidney function and dietary factors, many of which are well known and are adjusted for, during clinical trials, and also factored into calculations concerning drug dosing. These variables are the reasons that are used to explain why different patients may respond differently to the same drug. They are the reasons why, similar to several other biological processes, therapeutic outcome data are better described by statistical distributions, rather than discrete values.

Genetic factors offer a significant contribution to inter-patient drug response variability. Estimates at quantifying this genetic contribution have ranged between 20% and 95% for different drugs.[7,8] Pharmacogenetics is the study of this genetic variability. Its aim is to establish algorithms and models which could be used to associate DNA variations with specific therapeutic outcomes, and therefore use the former to predict the latter. Pharmacogenomics offers a more global approach, and encompasses the study of variations of DNA and RNA characteristics as related to drug response. Such work is carried out using an "–omics" approach, i.e. using technologies that study the genome (DNA) or transcriptome (RNA) as a global entity rather than focus on localised small candidate regions of interest. The European Medicines Agency, in 2007[9], offered the definitions shown in Table 2, in order to better clarify the meaning of both terms. Table 3 lists common terminology used in the fields of genetics.

Table 2: Definitions of the terms "Pharmacogenomics" and "Pharmacogenetics" as approved by the European Medicines Agency.[9]

Pharmacogenomics (PGx) The study of variations of DNA and RNA characteristics as related to drug response.
Pharmacogenetics (PGt) The study of variations in DNA sequence as related to drug response.

What do pharmacogenetics and pharmacogenomics have to offer?

Throughout the years, the application of therapeutics has gradually shifted focus from the drug to the patient. The "one drug fits all" maxim is no longer valid, and each patient is now the fulcrum around which therapeutic options are specifically selected. Personalized medicine, has thus taken centre stage, and together with evidence-based prescribing, has contributed to significant ameliorations in patient management outcomes.

The application of pharmacogenomic knowledge, aims to expand personalized medicine, by providing a means by which a patient's most individualized variable, his DNA genome, can be used to predict therapeutic outcomes to specific drugs. Adverse effect profiles may also be similarly predicted. Such information has critical value for the selection of the best drug, as well as the best dose, for a particular patient. This can especially afford improved therapy outcomes in patients who are on narrow therapeutic window medications (e.g. anti-epileptic drugs, immunosuppressant agents, theophylline), patients who are being treated with medicines that take a long time to start demonstrating clinical efficacy (e.g. SSRIs) and patients who are on drugs that may exhibit serious adverse reactions (e.g. anti-cancer drugs, anti-retroviral therapy).

The occurrence of serious adverse drug reactions (ADRs), is of major concern in therapeutics, and the major reason for drug withdrawals from the market. A recent Liverpool-based study, reported that 14.7% of hospital admission patients experienced ADRs that were due to drugs that were initiated or continued during the hospital stay[10], while a Swedish-based study reported that 3.1% of deaths in the general population, are the cause of fatal adverse drug reactions.[11] ADRs which are due to genetic variation, and which were previously considered to be unpredictable, may now be preventable through pharmacogenetics. Recommendations for applying pharmacogenetic knowledge for ADR prevention include (a) consideration of alternative drugs, whose action is known not to be subject to the genetic variation in question, (b) dose reduction if the prescribed drug is mandatory, (c) advice to the patient to be extra careful to monitor for adverse effects early in therapy, and (d) particular avoidance of administering multiple drugs whose actions are influenced by the same genetic variations (e.g. avoid administering multiple drugs which are metabolised by the same CYP450 enzyme, in patients who carry a low-activity variant for that enzyme).[12] Table 4 lists a few examples of drugs whose adverse effects are well known to be pharmacogenetically dependent. A list of all drugs for which the FDA has requested labelling modifications in order to include pharmacogenetic information may be found on the FDA website.[13]

Ethnic genetic variability

Since pharmacogenetic prediction is based on the association of specific genetic profiles with specific drug responses, the differences in the types and frequencies of DNA variants found in different ethnic groups, often confounds the applicability of testing. For example, a pharmacogenetic test which has been developed from genetic polymorphism data in a Caucasian population, may have been optimized to genotype the 10 most common DNA variants which influence the rate of metabolism of Drug X. However, the Asian population, may only have a few of these variants, and indeed may have others which are not found in Caucasians. This often puts severe constraints on the extent to which pharmacogenetic tests may be put to use, and from a commercial aspect, limits the potential for worldwide distribution of the same testing kit or protocol. The implications of this also have to be seen in a society which is always becoming more and more multinational and multicultural.

How does pharmacogenomic knowledge arise?

Interindividual variations in the human genome are well known. For example, the SNP consortium, a group of ten large pharmaceutical companies and the U.K. Wellcome Trust, has identified about 1.8 million single nucleotide polymorphisms in the human genome.[14] The question which arises is, which of these have any importance to health? Which SNPs are relevant to disease, which are relevant to drug response, and which are completely harmless? And what about other types of genetic variation, such as DNA insertions, deletions and variable repeat sequences?

Initial pharmacogenetic studies have largely applied what is termed the "candidate gene approach." In order to identify how genetics could contribute to the observed interpatient variability to the response of a drug, scientists would need to have detailed knowledge of the mechanism of action of the drug, and then intelligently

Table 3: Common terminology used in genetics

Allele	One of two or more gene variants
Candidate gene	A gene, selected on the basis of being considered important in a particular biological process, and therefore a potentially useful target to study with respect to that process.
DNA microarray	A technique to simultaneously measure several thousand potential alterations within a DNA sample.
Genetic marker	A known location on DNA that can assayed and used, together with several other genetic markers, to characterise an individual. A panel of genetic markers may be used as a "fingerprint" for a particular DNA sample or individual.
Genotype	The genetic makeup of an organism, usually referring to the presence or absence of one or more polymorphisms or mutations.
GWAS	Genome wide association study. A technique to identify which regions in a genome might be responsible for specifically observed features (such as a particular disease or drug response) within a population.
Mutation	A DNA variant sequence that occurs at a frequency of less than 1% in the general population
Polymorphism	A DNA variant sequence that occurs at a frequency of 1% or more in the general population
Phenotype	Features of an organism, which can be measured or observed, such as disease, body weight, response to a drug, eye colour etc.
SNP	Single nucleotide polymorphism. A DNA variation in which one DNA base is substituted by another.

Table 4: Examples of drugs for which pharmacogenetic variability is known to influence the risk of adverse effects[13,39]

Drug	Gene/s involved	Potential adverse effect
Abacavir	HLA-B*1502	Increased risk of general hypersensitivity
Azathioprine	TMPT	Slower metabolism and greater risk of myelotoxicity
Carbamazepine	HLA-B*1502, CYP1A2	Increased risk of severe dermatological hypersensitivity reaction
Carvedilol	CYP2D6	Increased risk of adverse effects in slow metabolizers
Clopidogrel	CYP2C19	Reduced metabolism of the pro-drug clopidogrel, lower exposure to the active metabolite and lower therapeutic effect
Fluoxetine	CYP2D6	Increased risk of toxicity in slow metabolizers, especially if prescribed with other CYP2D6-metabolized drugs
Irinotecan	UGT1A1	Slower metabolism and increased risk of neutropenia
Isoniazid	NAT2	Increased risk of agranulocytosis, hepatotoxicity and seizures
Nilotinib	UGT1A1	Exacerbation of drug-induced jaundice
Rifampicin	NAT	Slower metabolism and greater risk of general adverse reactions
Warfarin	CYP2C9, VKORC1	Reduced metabolism and higher bleeding risk

select critical steps in the pathway to study genetically, based on the presumption that such steps are where it is most likely that genetic variability might have a phenotypic response. Any identified polymorphisms have then to be studied from a functional aspect, in order to prove that this variability is indeed responsible for the observed drug response variation. This has generated considerable valid data and indeed up to about 10 years ago, published studies in the pharmacogenetic scientific literature are largely based on such approaches. However the failure to identify pharmacogenetic variability cannot be underestimated in such studies. The fact is that we do not know all the mechanisms of action of every drug, and a cursory look through any scientific literature database will show that even today, scientists are still identifying novel pathways for therapeutic or adverse effects of established drugs which have now been marketed for several years.

With the advent of new research technologies, the candidate gene approach has now been making way for a newer *pharmacogenomic* approach, which does not rely on prior knowledge of mechanism of drug action. This approach is based on what are termed genetic *association* studies, and from a pharmacological knowledge aspect, only require the clinical ability to be able to stratify patients into separate categories, based on how they respond to a particular drug. A group of patients, may for example, be prescribed a drug, and based on the therapeutic outcome, be grouped into poor responders, normal responders and high responders. A DNA sample from each patient is then screened for thousands of *genetic markers* spread throughout the whole genome, using a technological approach called a *DNA microarray* system. These markers are actually regions of DNA that have been well localized and studied, are known to be polymorphic (ie are likely to be different in different individuals), and are distributed throughout the whole genome. The most common type of markers used, are indeed SNPs. For the purposes of association studies, such markers may be compared to thousands of signposts, spread throughout the whole genome, with the technological ability for the message on every individual signpost to be accurately assayed and read using microarrays. The marker data from each patient is then analysed statistically, with the aim of identifying a small set of DNA markers that are statistically *associated* with a particular patient response group for the drug under study. Since these DNA markers can be easily genotyped, this approach generates a shortlist of DNA markers

Table 5: Drugs for which dose adjustment could be considered based on Amplichip® CYP450 assay results

Drugs which are substrates for CYP2D6	
□-blockers	Carvedilol, metoprolol, propafenone, timolol
Anti-depressants	Amitriptyline, clomipramine, desipramine, imipramine, paroxetine, venlafaxine
Antipsychotics	Haloperidol, risperidone, thioridazine
Opioids	Codeine, dextromethorphan, tramadol
Others	Atomoxetine, flecainide, mexiletine, ondansetron, tamoxifen
Drugs which are substrates for CYP2C19	
Proton pump inhibitors	Omeprazole, lansoprazole, pantoprazole
Anti-epileptics	Diazepam, phenytoin, phenobarbitone
Others	Amitriptyline, clomipramine, cyclophosphamide, progesterone

(essentially DNA polymorphisms) which can be assayed for any new patient, and which are statistically robust to be able to be used to predict into which therapeutic category (poor, normal or high responders, in this example) the patient will fall. This approach forms the basis of what are known as pharmacogenomic genome wide association studies (GWAS). Although more expensive than candidate gene approaches, GWAS have the advantage of not relying on the extent of available pharmacological knowledge of drug action, and have a higher success rate in establishing genetic profiles which are predictive of therapeutic or adverse reaction outcomes.

Pharmacogenetics, pharmacogenomics and pharmacy

Perhaps one of the greatest challenges of science is to bridge the gap between theory and practice. Rather than simply a matter of education, this is often more a question of implementation. Professionals within a health care system need to be informed about new therapeutic potentials, they need to be given access to information they can assimilate and they also need to be part of the implementation process of any novel tool. Both pharmacists and medical doctors need to understand, appreciate, and advise; and be knowledgeable enough to apply emerging pharmacogenetic principles, and interpret their outcomes.

"The main role of pharmacists within both primary and secondary care, is to supply medicines and to ensure this medication is appropriate for the individual and taken safely."[15] Within this context, pharmacists will need to take on new roles in the realm of pharmacogenetics, and should be in a position to pioneer the introduction of new tools as they are made available. This may not only require occasional participation at appropriate structured educational programmes, but also personal initiative to keep up to date with this rapidly developing field. As early as 2003, it was already recognised in the UK, that the level of genetics in most pharmacy undergraduate curricula was insufficient to empower newly emerging pharmacists with the skills required for the future.[16] Similar observations were also made on pharmacy curricula in the US, at around the same time.[17,18] Pharmacogenetics is unfortunately still often viewed by academic curriculum planners, to be an intellectual area of study, with few current practical implications, and is therefore relegated to a lower priority level than, for example, pharmacodynamics and pharmacokinetics, both of which are widely recognised to merit a serious understanding, if one is to appreciate therapeutic and toxicological drug actions. However, as early as 2002, a US questionnaire-based study carried out amongst various health care professionals, had already identified a high level of awareness that Pharmacogenetics will be useful to "identify patients who will respond to a medication", it will "identify patients who are at high risk for adverse drug events and it will help to "determine a medication's place in therapy."[19]

Perhaps one reason for the relative low direct health care professional involvement at the current time, is the specialization of therapeutic areas in which clinical applications of pharmacogenetic testing are currently available. The translational period from bench to bedside is naturally long, and as expected, priority has been afforded to therapeutic areas for which it is more critical for outcomes to be optimized, such as oncology. This effectively places the focus of pharmacogenetics on hospital and specialized clinics, and less on the community. Such focus is however expected to change, as more evidence for the benefits of genotype-guided prescribing emerges, and more pharmacogenetic tests become available.

Indeed, the 2006 report entitled 'Realising the Potential of Genomic Medicine', published by the Royal Pharmaceutical Society of Great Britain[20], already highlighted the importance of augmenting the pharmacists' professional knowledge of pharmacogenetics and molecular medicine, in order to be prepared for new pharmacogenetic roles. Such roles may vary according to the pharmaceutical setting. Pharmacists working in drug development may be involved in the design and execution of pharmacogenetic arms of pre-marketing clinical trials, hospital clinical pharmacists may be involved in the prescription of pharmacogenetic tests, while community pharmacists might be more involved in providing information and advice on drug use, in connection with already available patient pharmacogenetic test results. In all cases, a sound knowledge of pharmacogenetic approaches, together with training in the correct interpretation of a pharmacogenetic test result, and its significance in pharmaceutical practice, is mandatory.[21]

Pharmacogenetics and pharmacogenomics in practice

Translational pharmacogenetics / pharmacogenomics is evolving. As selected pharmacogenomic biomarkers are promoted from "exploratory" to "qualified" status[22], more approved tests will become available. The following are some robust examples of cases where pharmacogenetic testing has already been integrated into therapeutic drug use.

Izoniazid

Perhaps the earliest and most widely reported pharmacogenetic data, was that concerning the anti-tuberculous agent isoniazid (INAH). Isoniazid is a substrate for metabolism by acetylation through the actions of N-acetyltransferase type 2 (NAT2). The existence of fast and slow acetylating individuals has been known for decades, and interindividual variations in the INAH elimination half life of over 100% have been reported. INAH dose adjustment based on NAT2 phenotype status, has been well studied in the literature, and this was initially based on phenotypic differentiation identified by biochemical tests. Slow acetylators require dose reduction, in order to avoid development of potentially serious adverse drug reactions such as agranulocytosis, hepatotoxicity and seizures, while fast acetylators require increased doses to attain therapeutic efficacy.[23] Extensive NAT2 pharmacogenetic studies have now identified specific gene variants that are responsible for fast acetylators and slow acetylators, thus replacing phenotype testing with genotype testing as a basis for determination of INAH acetylator status.

Trastuzumab

Trastuzumab (Herceptin®) is a humanized monoclonal antibody against the HER2 tyrosine kinase receptor, which is overexpressed in 25-30% of breast cancers. HER2 overexpression (HER2+) is associated with enhanced tumour aggression. Clinical studies have shown Trastuzumab to be effective in HER2+ patients, but only exert insignificant effects in HER2- individuals. Thus the establishment of HER2 status has become an important determinant to the use of Trastuzumab. Modern approaches to determine HER2 status, today include immunihistochemistry to semi-quantitatively estimate the amount of HER2 proteins expressed on the surface of tumour cells, FISH (Fluorescence In-Situ Hybridization)

Table 6: Useful pharmacogenetics and pharmacogenomics websites. All listed websites are live as on 30 May 2011

European Medicines Agency Pharmacogenomics Working Party http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/CHMP/people_listing_000018.jsp&murl=menus/about_us/about_us.jsp&mid=WC0b01ac0580028d91&jsenabled=true
Food and Drug Administration Interdisciplinary Pharmacogenomics Review Group http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083889.htm
PharmGKB Pharmacogenomics knowledge base http://www.pharmgkb.org/
National Center for Biotechnology Information: One size does not fit all: the promise of pharmacogenomics http://www.ncbi.nlm.nih.gov/About/primer/pharm.html
The International Union of Basic and Clinical Pharmacology. Pharmacogenomics and Pharmacogenetics: Introduction http://www.iuphar.org/sections/PGx/sec_PGx.html
Nuffield Council on Bioethics. Pharmacogenetics: ethical issues. http://www.nuffieldbioethics.org/pharmacogenetics
National Institute of Health. National Institute of General Medical Sciences. NIH Pharmacogenomics Research Network. http://www.nigms.nih.gov/Research/FeaturedPrograms/PGRN/
NHS, UK. National Genetics Education and Development Centre. Teaching pharmacogenetics. http://www.geneticseducation.nhs.uk/teaching-genetics/pharmacogenetics.aspx
PHG Foundation interactive tutorials. Pharmacogenomics. http://www.phgfoundation.org/tutorials/pharmacogenomics/index.html

to determine the number of copies of HER2 genes in tumour cells, and the SPoT-Light HER2 CISH (Subtraction Probe Technology Chromogenic In Situ Hybridization) test, which also detects the number of HER2 gene copies in cancer cells, but is simpler to perform that FISH, and was approved by the FDA as a HER2 screening test in 2008.[24]

Substrates of CYP2D6 and CYP2C19

The two major cytochrome P450 enzymes, 2D6 and 2C19 are estimated to contribute to the metabolism of approximately 25% of currently used prescription medicines in Europe. These enzymes are highly polymorphic, and several variants of their genes exist. Some gene variants result in enzyme proteins with similar activity to wild type, but most are responsible for enzymes with higher or lower activity than normal. Indeed, some variants produce an enzyme with no activity at all. Specific technical details may be found through the Human Cytochrome P450 Allele Nomenclature Committee.[25] Therefore the rates of metabolism of drug substrates for CYP2D6 and CYP2C19 are greatly dependent on the particular gene variants which an individual is carrying.

Excessive or prolonged therapeutic effect or even drug-related toxicity may follow administration of a *typical* dose to a patient who carries a low-activity variant, by failing to metabolize the drug at the expected rate. Conversely, a patient with a high activity variant, may metabolize the drug at a faster rate than normally expected, and may be therefore potentially unable to maintain therapeutic window concentrations of the drug, at conventional dosing regimens. Adjustment of drug dosage could therefore be required, based upon knowledge of CYP2D6 and CYP2C19 genotypes.

In view of this, Roche® developed a DNA microarray assay (using Affymetrix® technology) that genotypes for 27 selected CYP2D6 and 3 selected CYP2C19 gene variants, and based on this data, predicts the metabolizer status of the individual. The test generates a predicted phenotype of ultrarapid, extensive, intermediate or poor metabolizer status, for CYP2D6 and extensive or poor metabolizer status for CYP2C19. Table 5 lists a selection of CYP2D6 and CYP2C19 substrates, which Roche® recommends be suitable predictive targets for the application of this test. The Amplichip test was approved by the FDA in 2004.[26]

Irinotecan

Irinotecan is a topoisomerase I inhibitor anti-cancer drug, normally used in combination with other chemotherapy agents. Its main indication is colon cancer, and patients may experience severe diarrhoea, neutropenia and immunosuppression as relatively common serious adverse effects. Following administration, the drug is initially hydrolysed to its active metabolite SN-38, and subsequently inactivated in the liver by the enzyme uridine diphosphate glucoronosyltransferase 1A1 (UGT1A1). This latter inactivation step, is under the influence of a much studied promoter DNA variant which involves the insertion of an additional TA dinucleotide in a tandem repeat sequence. Patients carrying this variant, known as UGT1A1 allele 28 (UGT1A1*28, $(TA)_6$>$(TA)_7$), produce less UGT1A1 than normal, and therefore take longer to metabolize irinotecan than expected. Such patients are at a higher risk of potentially fatal irinotecan toxicity.[27] This has led to the commercialization of an FDA-approved UGT1A1 genotyping assay[28], and an FDA approved amendment to the official prescribing information which states that "Individuals who are homozygous for the UGT1A1*28 allele (UGT1A1 7/7 genotype) are at increased risk for neutropenia" and that "when administered in combination with other agents, or as a single-agent, a reduction in the starting dose …. should be considered for patients known to be homozygous for the UGT1A1*28 allele." [29]

Warfarin

Warfarin is a prime example of a commonly used drug, possessing significant inter-patient response variability, a narrow therapeutic window, and the potential to adversely interact with a wide range of concomitantly administered medicines. Patients on warfarin need to be regularly and individually monitored using the international normalized ratio (INR) as

an index of warfarin efficacy, and doses need to be regularly optimized in order to maintain effectiveness and minimize adverse reactions.

Published studies have suggested that over 40% of interindividual warfarin dose variability can be predicted by SNPs in the VKORC1 (1639G>A and 1173 C>T alleles) and CYP2C9 (CYP2C9*2 and CYP2C9*3 alleles) genes. VKORCI codes for subunit 1 of the warfarin target, Vitamin K epoxide reductase complex, while CYP2C9 partakes in the metabolism of both R- and S-warfarin enantiomers. Carriers of variant alleles are at higher risk for bleeding complications,[30] particularly at induction of warfarin therapy, and genotype-guided dosing algorithms have been shown to be safer and more effective at estimating the maintenance warfarin dose rather than INR monitoring alone.[31]

Pharmacogenetics practice points for pharmacists

- DNA variations may be responsible for inter-patient differences in drug efficacy and toxicity.
- One specific DNA variant may influence the response of several drugs.
- Variations in genes which code for drug receptors, drug transporters, metabolising enzymes, and proteins involved in signalling pathways may be especially relevant.
- Pharmacogenetics aims to predict drug response from patient genotypes, and therefore provide a tool for personalized optimization of drug and dose selection.
- A specific pharmacogenetic test is usually only applicable to the population for which it was developed, and not to other ethnically diverse groups.
- The correct interpretation of some pharmacogenetic tests may require prior genetics-based knowledge and training.
- The EMA and the FDA are both actively involved in ongoing developments, through the establishment of the PgWP and IPRG groups.

Regulatory issues

The year 2005 saw the establishment of the European Medicines Agency Pharmacogenetics Working Party (PgWP; this later changed its name to the Pharmacogenomics Working Party)[32] and the Food and Drug Administration Interdisciplinary Pharmacogenomics Review Group (IPRG).[33] Both groups work jointly, to prepare guidelines and provide advice; and extensive information about their activities can be found on their respective websites.[34] One of the major actions of these groups has been the establishment of "Voluntary Exploratory Data Submission" (VXDS) procedures (previously called "Voluntary Genomic Data Submission" or VGDS). VXDSes constitute pharmacogenomic submissions that are not required as part of a regulatory submission, and therefore are not part of the regulatory decision making processes. They provide a platform through which industry is encouraged to voluntarily submit pharmacogenomic data to the EMA / FDA, with the aim of benefitting from an enhanced mutual understanding of relevant scientific issues. Such understanding "may prevent delays in reviews of future submissions where genomics are an integral part of specific studies in a drug development program."[33] VXDS submissions address areas such as the genetic loci or gene expression profiles being explored, the test systems and techniques employed, the application of pharmacogenomic testing during drug development, procedures for transmitting, storing, and processing large complex data sets, and bioinformatics software development.[22] The first joint FDA / EMEA document, detailing the general principles to be applied in processing joint FDA / EMEA VGDSes was issued as early as 2006[35], just one year after the establishment of the PgWP and IPRG working groups.

Clinical implementation of pharmacogenetics

The Pharmacogenomics Research Network of the National Institutes of Health, USA, set up a Clinical Pharmacogenetics Implementation Consortium (CPIC) in 2009, with the aim of addressing the "need for very specific guidance to clinicians and laboratories so that pharmacogenetic tests can be used wisely in the clinic." In its two years of existence, the CPIC has set up frameworks aimed at "understanding the types and levels of evidence needed to justify incorporation of pharmacogenetics into clinical practice." In particular, CPIC assign importance to the following considerations (a) a sound scientific rationale linking genomic variability with drug effects, (b) the therapeutic index of the involved medications, (c) the severity of the underlying disease, (d) the availability of alternative dosages or drugs for patients with high-risk genotypes, (e) the availability of approved laboratory tests, and (f) the availability of peer-reviewed clinical practice guidelines that incorporate pharmacogenetics in their recommendations. Electronic databases are set to be critically instrumental for such implementation, together with decision-support tools which will aim to integrate database information with laboratory pharmacogenetic test results. This can provide a platform through which genetic data can be translated to clinical practice.[36]

Future developments could see actual genetic testing moving out of the laboratory and into the clinic. The Imperial College, London, and its spinout company DNA Electronics, are currently developing a novel handheld device that provides on-the-spot pharmacogenetic testing. This device, called the "SNP Dr" uses DNA from saliva or cheek swab samples as a template for analysis, and performs rapid SNP assays based on a novel silicon chip technology, to provide "while you wait" pharmacogenetic predictions.[37] Such technology, will undoubtedly accelerate the integration of pharmacogenetic principles within rational prescribing practices.

Conclusion

Pharmacogenetics is an evolving discipline. The ongoing co-operation of basic and clinical research with evidence-based science and regulatory frameworks will help to achieve controlled implementation of a system which is working to provide new tools for improved therapeutic outcomes, and safer prescribing patterns. Table 6 lists some relevant websites, for further reading.

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