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Pharmacogenomics: The Scientific Basis of Rational Drug Development and Prescribing

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Abstract

"It is more important to know what sort of a patient has a disease than what sort of a disease a patient has" (Hippocrates 460 BC-370 BC).

The holy grail of drug discovery is to ensure that an individual responds positively to an investigational drug with minimal or no adverse events. This could then translate to newly discovered drugs being licenced for prescribing as safe and effective therapeutics. Pharmacogenomics may herald the technology for this aspiration to become reality.

Uniting the disciplines of pharmacology and genomics, pharmacogenomics provides a mechanism to understand and predict the response of an individual to a drug or group of drugs. This is based on the premise that an individual's genotype affects the pharmacokinetics, pharmacodynamics and, ultimately, the individual's their response to a drug.

This review will begin by reviewing the history of drug development and then proceed to discuss the use of pharmacogenomics in drug development through case studies in oncology, respiratory and vaccinology. It will then go on to discuss how pharmacogenomics presently influences prescribing practices and how this technology may have the potential to enhance patient safety when medicines are administered.

Keywords Pharmacology; Genomics; Pharmacokinetics; Pharmacodynamics

Historical Perspective of Drug Development and Pharmacogenomics

The observation that individuals react differently to exogenous agents dates back to Ancient Greece 510 BC, where Pythagorus observed the differential effects of Fava bean consumption on individuals [1]. It was, however, not until 1956 that glucose-6-phosphate enzyme deficiency was recognised as the culprit for "Favism" and, additionally, the sensitivity to drugs such as primaquine [2].

Also in the 1950s, a German physician, Friedrich Vogel, first coined the term "pharmacogenetics". This initially concentrated on explaining the unexpected response to drugs related in relation to an individual's genetic makeup, (which usually relates to metabolism) and explored the genetic variation in a population or variations specific to a disease. It applies genomic technologies to help develop new therapeutics and potentially categorise existing therapeutics [3]. Thereafter, the completion and publication of the human genome opened the possibilities for a new era of drug discovery and personalised prescribing [4,5].

Pharmacogemonic Approaches to Drug Development and Clinical Trials

The human genome consists of approximately 3.3 billion base-pairs and the difference between any two individuals in terms of DNA sequence is just 0.1%; it is this difference that influences disease susceptibility, progression of disease and response to drug intervention [6,7]. A solid platform for a rationalised drug discovery programme emerged with the completion of the human genome project and rapidly advancing technology.

The pharmaceutical industry applies the principles of pharmacogenomics in the drug discovery programmes they oversee; it also undertakes in-depth evaluation of target gene sequences to determine genetic heterogeneity in different ethnicities with the same disease to tailor clinical trials and licensing license drugs for of the drug in appropriate individuals. Additionally, they may use genetics to "homogenise" a disease subpopulation in early proof of concept studies. In later studies/post-licensing, knowledge of genetic polymorphisms may be utilised to predict safety and efficacy of new medicines.

Pharmacogenomics in Oncology

Original cancer treatments took a "one-size-fits-all" approach where generic cytotoxic were developed and prescribed as chemotherapy to all cancers. Over the last decade, the discovery and development of cancer drugs has changed to a pharmacogenomic approach. Identifying the heritable differences responsible for either the

occurrence of toxicity or lack of efficacy potentially reduced reduces the unpredictability of cancer treatments.

An example of this personalised approach to therapies involves the Epidermal Growth Factor Receptor (EGFR).

EGFR is one of the more extensively studied growth factor receptors and has been, which have been implicated to play a role in the pathogenesis of human malignancies. EGFR is a membrane spanning 170-kDa glycoprotein and stimulates cell proliferation after ligand binding and receptor dimerization [8,9]. Aberrant signalling of EGFR contributes to the oncogenic phenotype of more than 50% of nNon-small cell lung cancers (NSCLC). Hence drugs that target EGFR and inhibit its activities have been developed.

Two main classes of EGFR inhibitors have been developedare currently available: Tyrosine-Kinase inhibitors (TKI) eg. eErlotinib [10,11] and monoclonal antibodies eg. cCetuximab [12]. Pharmacogenomic studies have shown that mutations in the genes encoding EGFR can affect the mutation status of EGFR is associated with erlotinib efficacy. Nearly 90% of EGFR mutations are exon 19 deletions and exon 21 L858R point mutations. The crystal structures of the L858R and G719S TKI-sensitive EGFR mutants show that these substitutions activate the kinase through disruption of autoinhibitory interactions, resulting in receptors with 50-fold more activity compared with their wild-type counterparts. EGFR G719X (G719C, G719S and G719A) and L861Q mutations seem to confer sensitivity to EGFR TKIs such as erlotinib and gefitinib [13-15]. The response rate of TKIs has been reported to be 70% with a progression-free survival of 9-13 months [13]. Interestingly, the response rates to the monoclonal antibody have, to date, not been found to be correlated to genetic mutations in EGFR but only to the expression of this receptorreceptor expression.

Despite great improvements in the progression free survival, there is still an unmet need to treat non-responders and those that relapse and develop resistance to standard treatments. Hence using pharmacogenomics to elucidate mutations, drug targets of down-stream signalling pathways of EGFR such as KRAS, PI3K, PTEN have been developed and improvements made for the therapeutic options in subsets of patients with treatment resistant NSCLC [16].

Pharmacogenomics in Respiratory Disease - Asthma

Asthma is a complex disease consisting of multiple genetic and environmental factors; hence, treatment, therefore, is likely to be influenced by a large number of different pharmacogenetics loci interacting across pathways. A number of drug intervention studies have utilised pharmacogenetics to evaluate pharmacodynamics endpoints such as lung function, symptom severity, and asthma exacerbation frequency. These predetermined trial endpoints are have been analyzed for genetic associations on completion of the clinical trials.

There are, however, studies using a prospective, genotype-stratified approach where DNA is collected and genotyped for a variant of interest before trial recruitment and forms the basis for randomization to drug or placebo. BARGE (Beta-Adrenergic Response by Genotype) of regularly scheduled albuterol treatment is an example of such a prospective genotype-stratified trial in asthma [17]. In this study, patients with mild asthma were enrolled on the basis of clinical criteria and their genotype (Arg/Arg or homozygous for glycine [Gly/Gly]) at the locus encoding the 16th amino acid of the β2-adrenergic receptor. Previous retrospective studies had suggested that this polymorphism was associated with adverse effects of β-agonist use in asthmatic patients [18,19]. The BARGE study found that patients with the Arg/Arg genotype improved when β-agonist therapy was withdrawn and replaced with ipratropium bromide.

Targeting of biological pathways in asthma is an avid avenue of drug discovery. The interleukin (IL)-4 and IL-13 pathway mediate Th2 lymphocyte-mediated allergic inflammation by binding and activating a common subunit of the IL-4 receptor, the IL-4α receptor subunit. A molecular inhibitor of the IL-4α receptor subunit, pitrakinra, and a monoclonal antibody, dupilumab, have been shown to be effective in preventing loss of symptom control in asthma subpopulations, characterized by increased blood or sputum eosinophils. Both biologic drugs block the IL-4α receptor subunit (encoded by IL4RA), resulting in dual inhibition of a shared IL-4 and IL-13 pro-inflammatory pathway.

In a dose-ranging study of pitrakinra, a significant dose-response in asthmatics with a specific IL4RA variant genotype (GG of rs8832, nearly one-third of the cohort) was noted while no dose response was observed in subjects with the remaining genotypes (AG or AA at allele rs8832) [20,21]. This clinical trial was an example of how a pharmacogenetic biomarker can identify a subgroup of responders embedded within an overall cohort that were which was unresponsive to a drug.

Investment to elucidate further pharmacogenetic loci could identify new drug targets in asthma and help inform confirmatory clinical trial design to select the asthma subtypes to assess response to pharmacological interventions.

Pharmacogenomics in Vaccinology

The goal of vaccinology is to discover, develop, and deploy highly immunogenic and safe vaccines that protect against infectious diseases in essentially 100% of the population. Twin studies provide opportunities to explore genetic contribution to vaccine response and to identify specific gene polymorphisms. Such studies, using cohorts of monozygotic and dizygotic twins, have been utilised in order to estimate the genetic and environmental contributions to variation in total immunoglobulin levels and specific IgG antibody levels to pneumococcal capsular polysaccharides showing that total IgG, IgA, IgM and isotype antibody titers were significantly correlated between monozygotic but not dizygotic twins [22]. Other studies have observed a high heritability for antibody responses to hepatitis B (77%), oral polio (60%), tetanus (44%) and diphtheria (49%) vaccines [23]. Additionally, for the conjugate Haemophilus influenza b (Hib) vaccine MZ and DZ twin pairs in Gambia were compared and heritability to antibody responses was estimated to be 51% indicating a genetic contribution in the immunogenicity response to this vaccine [24]. Single nucleotide polymorphisms in signalling lymphocyte activation molecule (SLAM) and CD46 have been discovered that are associated with variations in immune responses to the measles–mumps–rubella vaccine [25]. This highlights the importance in understanding the immunogenetics of measles vaccine receptors and how this correlates with variations in immune responses to vaccines, which could ultimately leading to the design of better vaccines. A future aspiration would be to design personalized vaccines based on the complex interactions of host genetic, environmental and other factors controlling the immunogenicity of vaccines.

Future Perspectives of Drug Development

Use of genetic data during drug development phases has the potential to identify novel targets, to predict Pharmacokinetic (PK)/ Pharmacodynamics (PD) variability. It also allows for the design of clinical trials, which maximise safety and therapeutic outcomes for patients.

The main challenge to applying pharmacogenomics to drug development results from the complex characteristics of polygenic diseases and the impact of environmental stimuli on the disease. The relationship of genetic and environmental factors may not be a simple additive one, but a complex (ecogenetic) interaction, requiring careful statistical assessment of interaction terms. Additionally, the polygenic nature of common complex diseases means that disease causation attributable to genetic contributors represents the aggregate effect of several genes and genetic heterogeneity means that multiple genes in different combinations may contribute to an apparently identical clinical presentation.

However, despite these challenges, drug-discovery programmes would benefit from investing and incorporating pharmacogenomics in early clinical development programmes to help define Go/No Go decisions and also to help define the population that would most likely derive benefit from the drug.

Therapeutics in the Clinic: Rational Prescribing

It is the aspiration of a prescriber to ensure that the medication administered to a patient has optimal efficacy and treatment. Present prescribing practice is based upon extrapolating results of a therapeutic trialled in a population. A limitation of this practice is that medications can have variable affects effects both in terms of efficacy and safety on individuals diagnosed with the same disease. Hence a customised approach to drug therapy has the potential to produce optimal safety and efficacy to an individual [26].

Successful use of pharmacogenomics customised medicines will allow physicians to: (1) select patients for drug therapy before writing a prescription; (2) exclude patients from drug therapy before writing a prescription (based on predicted toxicity or poor response); (3) select the optimal individual dose and dosing regimen; and (4) evaluate the genetic basis for an adverse event.

Predicting Response to Therapy

The variability between individuals significantly impacts the quality and cost of healthcare. The response rate of a major drug for a particular therapeutic area can vary considerably eg. 30% in Alzheimer's disease to 60% for cardiac arrhythmia control [27]. Hence the ability to increase the response rate of a group of individuals with a particular disease is highly desirable. Pharmacogenomics could be used as a tool to help achieve this outcome.

Anti-Platelet Agents

Anti-platelet medications are a widely prescribed drug class used in the primary and secondary prevention of thrombotic events associated with cardiovascular disease and cerebrovascular disease. Clopidogrel is one of the most commonly prescribed of these medications. It is a pro-drug requiring metabolism by CYP450 enzymes, particularly CYP2C19. There is an inter-individual response to the anti-platelet effect with clopidogrel. In a meta-analysis of nine studies involving cumulatively 9,685 patients, a significantly increased risk of the composite endpoint, cardiovascular death, myocardial infarction, or stroke was evident in carriers of one (HR 1.55, 95% CI 1.11-2.27, P=0.01) and two (HR 1.76, 95% CI 1.24-2.50, P=0.002) CYP2C19 reduced-function alleles. Similarly, there was a significantly increased risk of stent thrombosis in both carriers of one (HR 2.67, 95% CI 1.69-4.22, P<0.0001) and two (HR 3.97, 95% CI 1.75-9.02, P=0.001) CYP2C19 reduced-function alleles. These findings were so profound that the FDA issued a boxed warning relating to this in 2010 [28]. However, with the advent of newer agents such as pPrasugrel, (which is a pro-drug that does not require CYP2C19 metabolism), it may be prudent to test individuals at risk of thrombosis for genetic polymorphisms to appropriately determine prescription of an anti-platelet agent [29]. The present limitation to this rationalised approach is that to date there have been no randomised prospective clinical trials demonstrating that genotype-directed therapy is more effective than conventional approaches.

The Role of Pharmacogenomics in Avoiding Adverse Reactions

Adverse Drug Reactions (ADRs) are a major clinical problem that accounts for 6.5% of all hospitalisations and poses challenges in terms of patient well-being as well as an economic burden to healthcare budgets [30]. ADRs are also a major burden for the pharmaceutical industry; between 1990 and 2012, 43 drugs were withdrawn from the market due to severe ADRs [31].

Twin studies confirm that the rate of drug metabolism is heritable and hence pharmacogenomics can be used to assist the prediction of ADRs which can then inform the prescriber to avoid or dose reducer educe the dose of a therapeutic agent [32].

The enzyme, thiopurine methyltransferase (TPMT) catalyses the S-methylation of thiopurine, including 6-mercaptopurine and 6-thioguanine. TPMT activity exhibits genetic polymorphism and eight TPMT alleles have been identified to date. Three of these alleles, TPMT*2, TPMT*3A and TPMT*3C, account for 80-95% of intermediate or low enzyme activity [33,34]. If such patients are treated with standard doses of azathioprine (an immunomodulator used in leukaemias and autoimmune disease), they accumulate excessive thioguanine nucleotides in hematopoietic tissues, leading to severe haematological toxicity that which can be fatal.

An exemplar for the utility of a pharmacogenomic approach to rational prescribing is routine testing of the thiopurine methyltransferase genotype in patients with rheumatic disease prior to the prescription of the immunomodulator drug, azathioprine. In a study carried out by Black et al. it was reported that patients with rheumatic disease inheriting mutant thiopurine methyltransferase alleles were forced to discontinue azathioprine therapy within 1 month of initiating therapy because of serious haematological side effects [35]. The rate of abnormal liver function test results caused by azathioprine therapy was not associated with mutant alleles. Hence pre-testing of thiopurine methyltransferase genotype allows pre-therapy identification of patients at risk for serious toxicity from azathioprine and this is now a routine procedure in clinical practice.

Pharmacogenomics and Polypharmacy

In 2014, the RIGHT trial developed a protocol to test the concept that pre-emptive pharmacogenomic testing could guide clinical decision making for appropriate therapies, aspiring to the premise "Right Drug, Right Dose at the Right time." [36]. In collaboration with

the Mayo Clinic Centre for Individualised Medicine, over one thousand patients were identified from the Mayo Clinic Biobank using a multivariate prediction model with a high risk of initiating statin therapy within 3 years. The prediction model included age, sex, race, and 6 chronic diseases categorised by the Clinical Classifications Software for International Classification of Diseases, Ninth Revision codes (dyslipidemia, diabetes, peripheral atherosclerosis, disease of the blood-forming organs, coronary atherosclerosis and other heart diseases, and hypertension). Pre-emptive pharmacogenomic testing of this group included CYP2D6 genotyping and targeted sequencing of 84 pharmacogenomes that had FDA warnings for drug interactions. The genomic results were entered into the individuals' electronic medical record (EMR) and if a drug was prescribed for the individual potential patient-specific, drug-gene interactions would be flagged.

Following on from this, in a very recent publication revealed that in this RIGHT cohort of 1,013 subjects, tested for five well-characterized pharmacogenomic genes (CYP2D6, CYP2C19, SLCO1B1, CYP2C9, and VKORC1), 99% of the participants carried a pharmacogenomics variant that could impact on the metabolism, effectiveness and side-effect profile of a given drug [37,38]. It will be very interesting to see how a longitudinal follow up from this "RIGHT" initiative will impact on the appropriate prescribing of therapeutics. Further clinical trials are required and will be essential in adding support behind the initiative of pre-emptive genotyping in clinical practice.

Future of Pharmacogenomics

The aspiration of personalised therapeutics is likely to be a reality in the next decade. The applications of technologies including molecular biology, molecular genetics and genomics, will impact our understanding of health and pathology. In turn this can interface with our understanding of drug action through applying pharmacogenomics. The interface between these concepts with the discovery, development and application of new medicines will be essential for the future progress of biomedicine and health care.

In conclusion, applying pharmacogenomics to the practice of clinical medicine may inverse Sir William Osler's notion: "If it were not for the great variability among individuals medicine might as well be a science and not an art (1892)".

Conflicts of Interest

Sonya Abraham has no conflicts of interest to declare. Hannah Jethwa has no conflicts of interest to declare.

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