Journal of Molecular and Genetic Medicine

Halum et al., J Mol Genet Med 2016, 10:1
DOI: 10.4172/1747-0862.1000210

Research Article Open Access

An In-Depth Look at the Clinical Relevance of Pharmacogenetic Testing Ascertained

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Abstract

Background: Pharmacogenetics is the study of genetic influence on pharmacological response. Pharmacogenetic testing serves to identify the presence of genetic variants which may affect pharmacological outcomes, and allows for the selection of pharmacological therapy based on a patient's specific genetic make-up. Therefore, it has the potential to become an invaluable resource in certain fields of medicine to provide patient-tailored pharmacotherapy to patients.

Objective: To determine the clinical relevance of pharmacogenetic testing.

Methods: A systematic review was conducted from September 2013- November 2015 using the EMBASE and EBSCO host databases, identifying English language Cochrane reviews, controlled clinical trials, randomized control trials, meta-analyses and systematic reviews conducted on humans. Search terms pertaining to pharmacogenetic testing in the following medication classes: cardiovascular, oncologic, pain management, antiretroviral, and antidepressant were used. Selected articles were evaluated and assigned ratings based on the level of evidence present. A rating of "A" was assigned for high level of evidence, "B" for moderate level of evidence, and "C" for minimal level of evidence.

Results: The literature search resulted in a total of twenty-one selected articles of interest. Of these articles, seven were identified with an evidence rating of "A" and four articles with an evidence rating of "B".

Conclusion: Pharmacogenetic testing is relevant to clinical practice in certain situations. Its use provides health care providers with additional information which may enable them to treat patients more efficiently by preventing adverse reactions and anticipating therapeutic responses. A lack of prospective randomized control trials, ethical concerns, and a lack of provider knowledge pertaining to pharmacogenetic testing remain as barriers to routine pharmacogenetic testing in clinical practice. Despite these barriers, the future of pharmacogenetic testing is promising and expected to be welcomed by those whom are concerned with providing optimal pharmaceutical care.

Keywords: Pharmacogenetics; Clinical relevance; Patient-tailored care; Genetic testing

Introduction

According to Lesko and Schmidt, "variability is the law of life and as no two faces are the same, so no two bodies are alike, and no two individuals react alike and behave alike under abnormal conditions which we know as disease" [1]. The study of pharmacogenetics serves to explain variability in pharmacological response resulting from genetic differences. Pharmacogenetics is based on the observation of phenotypes and investigates variations in genes as they relate to drug metabolism. It allows for better comprehension of pharmacodynamics and pharmacokinetics, in order to reduce potentially harmful side effects [1]. The mainstay of pharmacotherapy involves giving the right medication at the right dose to the right patient in order to treat a specific disease state or condition. Personalized medicine is achieved through having a comprehensive understanding of how a drug works the pathology of the disease state, and drug response within individuals [1]. The idea of individualized medicine has been present for a number of centuries, such as the Egyptian Papyrus Ebers, which contained more than 800 prescriptions used to treat individual patients suffering from various medical ailments, such as asthma and cancer. The goal of individualizing therapy is to reduce the quantity and severity of side effects and toxicities while reaching the desired therapeutic effect for the patient, yielding the most beneficial health outcomes. Pharmacogenetics allows for selection of pharmacological therapy based on a patient's specific genetic make-up and, therefore, has the potential to become an invaluable resource in certain fields of medicine to provide patient-tailored pharmacotherapy to patients.

Studies propose that pharmacogenetic testing is the missing link to better health outcomes. However, evidence also exists contrary to that, stating that it is of little clinical relevance. Despite this conflicting evidence, the Food and Drug Administration (FDA) has approved more than 100 drugs with pharmacogenetic information included within their labels [2]. There are also a multitude of pharmacogenetic tests available to identify genes that may affect drug metabolism. Pharmacogenetic testing remains a topic of controversy with conflicting evidence. The objective of this systematic literature analysis was to examine the literature-based evidence, and determine the relevance of pharmacogenetic testing in clinical practice. While this discussion cannot cover all medications, it will focus on up and coming areas of pharmacogenetic research which are attracting significant attention. The areas of particular interest and controversy include: cardiology, oncology, pain management, anti-retroviral, and antidepressant medical regimens.

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Received March 02, 2016; **Accepted** April 20, 2016; **Published** April 24, 2016

Citation: Halum AS, Bhinder MTM, Shawaqfeh MS, Muflih SM (2016) An In-Depth Look at the Clinical Relevance of Pharmacogenetic Testing Ascertained. J Mol Genet Med 10: 210 doi:10.4172/1747-0862.1000210

Methods

The objective of this literature analysis was to identify evidence regarding the use of pharmacogenetic testing in clinical practice. A systematic review of literature (Figure 1) was conducted from September 2013- July 2015 using the EMBASE and EBSCO host databases, searching CINAHL and MEDLINE, identifying Cochrane reviews, controlled clinical trials, randomized control trials, meta-analyses, retrospective case studies, and systematic reviews conducted on humans. Results were further limited to English language, full-text articles published between the years 2005-2015. A variety of search terms pertaining to pharmacogenetic testing in the following medication classes: cardiovascular, oncologic, pain management, antiretroviral, and antidepressant were used. Search terms used included: pharmacogenetics, genetic testing, tamoxifen, warfarin, clopidogrel, beta blockers, CYP2C19, CYP 2C9, CYP3A4, CYP 2D6, APOE, VKORC1, abacavir hypersensitivity, benzodiazepines, etc. Initial search results produced 10,367 articles which were then filtered based on the above search criteria.

After the initial filtration process, articles were then reviewed to determine statistical and/or clinical relevance. Strength-of-Recommendation Taxonomy (SORT) was then used in order to evaluate the quality of each non-review article. The articles of interest were then assigned an evidence rating of "A" indicating a high level of evidence, "B" for moderate level of evidence, and "C" for minimal level of evidence. Based on the literary evidence contained in the selected articles, evidence ratings were then assigned to each of the selected medications of interest. Evidence rating of "A" was assigned to indicate a high level of evidence pertaining to the clinical relevance of pharmacogenetic testing, "B" for moderate level of evidence, and "C" for minimal level of evidence.

Results

The initial literature search to determine the clinical relevance of pharmacogenetics testing resulted in 10,367 potential articles of interest. From that we evaluated each article as described in the methods section, which resulted in a total of 21 selected articles. Our evaluation of the literature resulted in seven "A" rated articles and four "B" rated articles. The results of which can be found in Table 1.

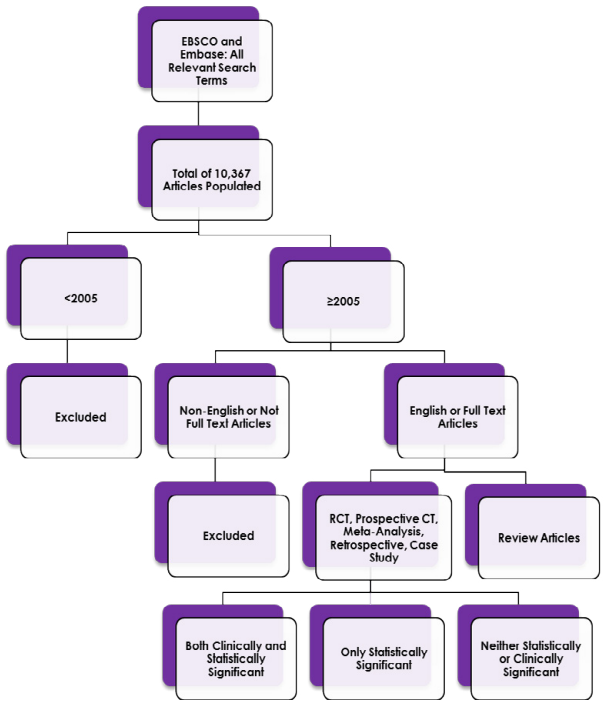

Figure 1: Article selection process.

Article	Evidence Rating
Clinical pharmacogenomics of Warfarin and Clopidogrel. J Shin	A
CYP2d6 and UGT2b7 Genotype and risk of recurrence in Tamoxifen treated breast cancer patients. J Rae et al.	B
Dosing Clopidogrel based on CYP2C19 genotype and the effect on platelet reactivity in patients with stable cardiovascular disease. J L Mega et al.	A
Effects of the CYP2D6 gene duplication on the pharmacokinetics and pharmacodynamics of Tramadol. J Kirchheiner	B
Effect of the CYP2D6*10 C188T polymorphism on postoperative tramadol analgesia in a Chinese population. Wang	B
Effect of genetic variants, especially CYP2C9 and VKORC1, on the pharmacology of Warfarin. E Fung	B
HLA-B*5701 Screening for hypersensitivity to Abacavir. S Mallal et al.	A
Influence of CYP2C9 and VKORC1 on Warfarin response during initiation of therapy. N A Limdi	A
Randomized and clinical effectiveness trial comparing two pharmacogenetic algorithms and standard care for individualizing warfarin dosing: CoumaGen-II. J L Anderson et al.	A
The analgesic effect of tramadol after intravenous injection in healthy volunteers in relation to CYP2D6. T Enggaard et al.	A
Clinical and genetic modifiers of long-term survival and heart failure. S Cresci et al.	A

Table 1: Article and corresponding evidence rating.

Findings included both positive and negative aspects of pharmacogenetic testing and its utility in clinical practice. Medications of interest included: warfarin, clopidogrel, beta blockers, abacavir, selective serotonin reuptake inhibitors, tamoxifen, tramadol, and HMG CoA reductase inhibitors, all of which currently contain pharmacogenomic information on their respective drug label. After evaluating the quality of each article, the level of evidence pertaining to each medication was assessed. Select medications, their respective biomarker of interest, drug label section as to where pharmacogenomic information can be found, as well as the assigned evidence rating is illustrated in Table 2.

Discussion

Based on the evidence obtained from the literature analysis, there are consistent findings that indicate genetic markers can assist in predicting drug effectiveness and prevent adverse drug reactions. However, how to implement this data into clinical practice remains unsettled. The field of pharmacogenetics is also facing challenges such as: the lack of reimbursement, liability concerns, insufficient medical training, insufficient sense of competence, and information overload. Another challenge is the ethical considerations, which should also be taken into account.

Several studies have been conducted pertaining to pharmacogenetics and, although many are contradictory, many have concluded that pharmacogenetic testing is necessary and recommended for certain medications. Medications of interest include cardiovascular, oncologic, pain management, anti-retroviral and antidepressant medications. Table 3 illustrates some of the common genes associated with polymorphisms that affect the pharmacokinetic and pharmacodynamic effects of select medications as well as the current recommendations for testing and therapeutic relevance [3].

Medication	Biomarker	Label Section(s)	Evidence Rating
Abacavir	HLA-B*5701	Boxed warning, contraindications, warnings and precautions, patient counseling information	**A**
Carvedilol	CYP2D6	Drug interactions, clinical pharmacology	**A**
Citalopram	CYP2C19/CYP2D6	Drug interactions, warnings	**C**
Clopidogrel	CYP2C19	Boxed warning, dosage and administration, warnings and precautions, drug interactions, clinical pharmacology	**A**
Metoprolol	CYP2D6	Precautions, clinical pharmacology	**C**
Pravastatin	APOE2	Clinical studies, use in specific populations	**C**
Tamoxifen	ER, Factor V Leiden, PT	Indications and usage, precautions, medication guide, warnings	**B**
Tramadol	CYP2D6	Clinical Pharmacology	**B**
Warfarin	CYP2C9, VKORC1	Dosage and administration, precautions, clinical pharmacology	**A**

Table 2: Pharmacogenetic biomarker and label section[a].

CYP2D6, CYP2C9	Metoprolol, tramadol, paroxetine, venlafaxine	Testing: **N** Therapeutic: **Y**
CYP2D6, CYP2C9, CYP2C19	Tamoxifen	Testing: **N** Therapeutic: **N**
CYP2D6, CYP2C19	SSRIs	Testing: **N** Therapeutic: **N**
CYP2C9, VKORC1	Warfarin	Testing: **N** Therapeutic: **N**
HLA-B*5701	Abacavir	Testing: **Y** Therapeutic: **Y**
CYP2C19	Clopidogrel	Testing: **N** Therapeutic: **Y**
CYP3A4	Statins	Testing: **N** Therapeutic: **N**

Table 3: Existing clinical practice guidelines for pharmacogenetic biomarkers. Recommendations given in the guideline regarding the utility of general pretreatment testing (testing) or regarding genotype-specific treatment (Therapeutic); N: guideline does not recommend testing or does not give recommendations; Y: guideline recommends testing or gives genotype-specific treatment recommendations [3].

VKORC1	CYP2C9					
	***1/*1**	***1/*2**	***1/*3**	***2/*2**	***2/*3**	***3/*3**
GG	5-7 mg	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg
AG	5-7 mg	3-4 mg	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg
AA	3-4 mg	3-4 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg	0.5-2 mg

Table 4: three ranges of expected maintenance of Coumadin (Warfarin). Lk daily doses based on CYP2C9 and VKORC1 Genotypes[a]. Ranges are derived from multiple published clinical studies. VKORC1 −1639G>A (rs9923231) variant is used in this table. Other co-inherited VKORC1 variants may also be important determinants of warfarin dose. [a]Data from: http://packageinserts.bms.com/pi/pi_coumadin.pdf [7].

Warfarin

Warfarin is an anticoagulant, which works by inhibiting vitamin K epoxide reductase complex subunit 1 (VKORC1), thereby decreasing the formation of vitamin K dependent clotting factors. It is indicated for prophylaxis and treatment of thromboembolic disorders, such as atrial fibrillation, deep-vein thrombosis, pulmonary embolism, prosthetic heart valves, stroke, and myocardial infarction. Although warfarin is widely used and effective for many, it does pose the risk of serious bleeding. Due to this, it has been assigned a Black Box Warning by the FDA (4). Dosing is complex and must be individualized and adjusted per patient specific lab values regarding coagulation. Genetic polymorphisms of interest pertaining to warfarin are CYP2C9 and VKORC, both of which result in variability in therapeutic response among individuals [4].

Warfarin is a racemic mixture containing an S-isomer and an R-isomer. Of the two isomers, it is the S-isomer that exerts the majority of warfarin's therapeutic effects. The S-isomer is primarily metabolised by CYP2C9. Polymorphisms of CYP2C9 have the potential to affect the metabolism of S-warfarin, leading to decreased clearance [4]. Based on the decreased clearance of the medication those individuals that possess the polymorphism would require lower doses of warfarin to achieve their therapeutic goal as compared to those with normal or "wild type" enzymatic activity. Variations of the CYP2C9 genotype account for 12% of the variability in dosing requirements between individuals, according to a meta-analysis of 12 studies [4].

The second gene of interest pertaining to warfarin is the gene that encodes for VKORC1. Different polymorphisms of this gene result in either higher dosing requirements or lower dosing requirements. A meta-analysis of 10 different studies concluded that polymorphisms of VKORC1 account for 25% of inter-individual variability in dosing requirements [4].

Identifying a patient's VKORC1 haplotype and CYP2C9 genotype are of clinical relevance as it may prevent adverse bleeding events and provide for improved medication efficacy. Currently, there are a number of different pharmacogenetic tests available for warfarin. Examples include, Rapid genotyping assay, Nanosphere verigene Warfarin metabolism nucleic acid test and the Warfarin dose advise genetic test, all of which have been approved by the FDA [5].

Several pharmacogenetic-based treatment algorithms have been proposed for warfarin. Table 4 illustrates a sample algorithm, which includes examples of maintenance daily doses of warfarin, according to different genotypes. Depending upon an individual's specific genotype, a dose reduction of 10% to 90% may be required [6,7].

Warfarin is one of the most extensively studied medications in the field of pharmacogenetics and several studies have shown that the use of pharmacogenetic testing in patients taking warfarin is clinically relevant. Despite this, the FDA does not yet recommend routine pharmacogenomic testing to determine dosing, but they do acknowledge that dose requirements are indeed influenced by CYP2C9 and VKORC1 and that when genotype information is available, it can be used to assist in the selection of a starting dose [5].

Clopidogrel

Clopidogrel is an oral anti-platelet agent indicated for the treatment and prevention of acute coronary syndromes, prophylaxis for thrombotic events, and unstable angina. It is a pro-drug which requires metabolism via hepatic enzymes into its active form, in order to exert its therapeutic effects. The enzyme CYP2C19 is greatly involved in the metabolism of clopidogrel to its active form [8]. Polymorphisms of this enzyme have been shown to have an effect on the therapeutic response of clopidogrel.

Polymorphisms of CYP2C19 can render an individual a poor metaboliser, meaning they have little to no CYP2C19 activity, and, therefore, are unable to metabolize clopidogrel to its active form when compared to those with normal or "wild type" enzymatic activity [8]. Individuals with polymorphisms of CYP2C19 who are receiving clopidogrel will have lower levels of the active metabolite resulting in decreased platelet inhibition, and are therefore at a higher risk of cardiovascular events [8]. Figure 2 illustrates an algorithm proposed

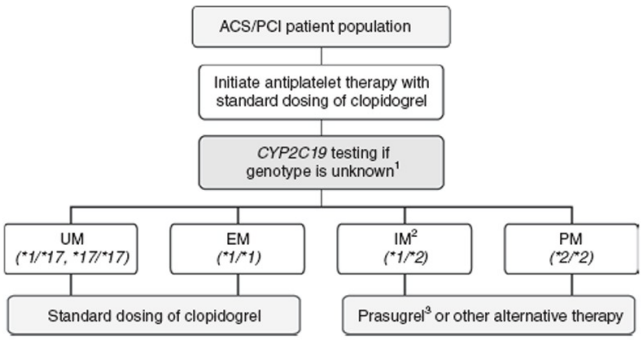

Figure 2: Algorithm to Initiate Anti-Platelet Therapy Based on CYP2C19 Genotype[a]. [a]Data from Johnson, Gong, Whirl-Amillo et al. [9].

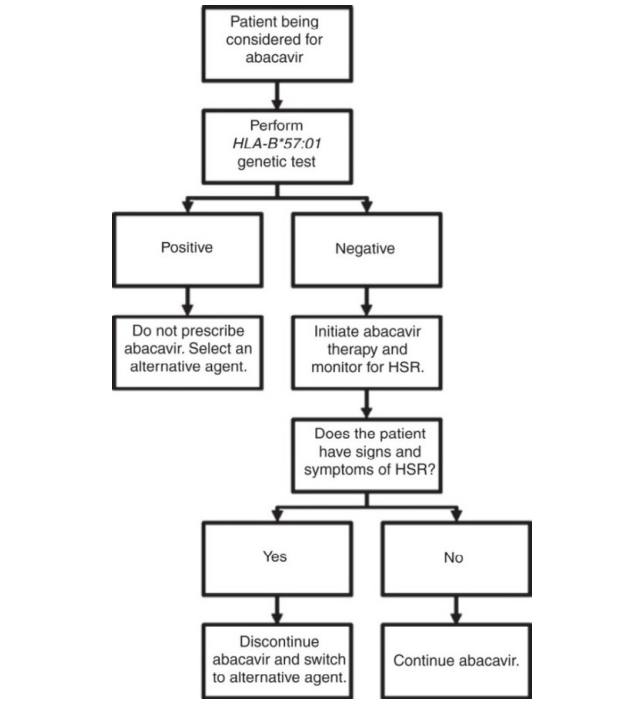

Figure 3: Treatment algorithm for clinical use of abacavir based on HLAB* 5701 genotype. HLA-B, human leukocyte antigen B; HSR, abacavir hypersensitivity reaction[a]. [a]Data by Klein Martin, et al. [16].

to initiate anti-platelet therapy in patients with acute coronary syndromes [9]. A recent multi-centre, randomized, double blind trial of 333 patients with cardiovascular disease concluded that patients with specific polymorphisms of CYP2C19 needed a dose increase from the typical 75 mg of clopidogrel to 225 mg to achieve similar anti-platelet activity as compared to those with normal CYP2C19 function [8].

Clopidogrel currently has an FDA boxed warning stating that poor CYP2C19 metabolisers may not benefit from this therapy and should consider an alternative treatment. Although evidence exists that this may be clinically relevant, routine testing is not yet recommended and there are no clear recommendations regarding dose adjustments in those who are poor metabolisers [8].

Beta blockers

Beta-blockers are a class of medication that antagonize beta adrenergic receptors and are indicated for the treatment and management of cardiovascular disorders including: hypertension, arrhythmias, myocardial infarction, heart failure, and angina. Examples of beta-blockers are: metoprolol, propranolol, and carvedilol, among others. The majority of the metabolism of beta-blockers occurs via CYP2D6 [10]. Metoprolol is the beta-blocker most heavily reliant upon CYP2D6 as it is responsible for 70-80% of its metabolism [10]. Although it is evident that polymorphisms of CYP2D6 affect the pharmacokinetics of metoprolol, several prospective cohort studies have shown that it does not appear to affect the efficacy or adverse reactions associated with this medication [10]. Prospective studies regarding metoprolol have also shown no difference in adverse reactions between those individuals categorized as poor metabolisers as compared to those who are not poor metabolisers [10].

Pharmacogenetic testing for CYP2D6 is currently available. AmpliChip CYP450 by Roch Diagnostics is an FDA approved test that can be used to determine the presence of polymorphisms and is able to determine if an individual is a poor or ultra-rapid metabolizer [5]. This test has the potential to assist providers when prescribing beta blockers as well as many other medications, however, beta-blockers have not received any specific recommendations for pharmacogenetic testing and evidence illustrates it to be of little clinical relevance.

HMG-CoA reductase inhibitors

HMG-CoA reductase inhibitors, or statins, are a class of drugs that lower the concentration of low-density lipoprotein cholesterol and are, therefore, used in the treatment of dyslipidemias. HMG-CoA reductase inhibitors include: rosuvastatin, atorvastatin, simvastatin, lovastatin, pravastatin, and fluvastatin. They are widely prescribed, but come with the risk of statin-induced myopathy. A genome-wide association study, SEARCH, found that a SNP in the SLC01B1 gene was associated with an increased risk of statin-induced myopathy in patients taking Simvastatin [4]. The gene influences the drug's serum concentrations and the hepatic uptake. It is presumed that these findings can be applied to other statins. This study also found a polymorphism in the CYP3A4 genome was found to require lower doses to reach optimal lipid control [4]. HMG-CoA reductase inhibitors have limited data on the usefulness of pharmacogenetic testing to predict statin-induced myopathies or reduced doses in those with a CYP3A4 polymorphism. Data supporting the use of pharmacogenomic testing for patients requiring statin therapy is also limited because not enough data proves it to be cost effective or clinically relevant [5]. The FDA does not currently recommend testing and its relevance is yet to be determined.

Selective serotonin reuptake inhibitors

Selective Serotonin Reuptake Inhibitors (SSRI's) are a class of medications used in the treatment of depression and anxiety disorders. Examples of SSRI's include citalopram, paroxetine, sertraline, and escitalopram among others. In general, the biomarkers of interest in regards to SSRI's are hepatic CYP enzymes, specifically CYP2D6 and CYP2C19. These enzymes are responsible for metabolising the majority of SSRI's and, therefore, polymorphisms of these enzymes have the potential to affect the clearance of these medications. A number of studies have shown that individuals identified as poor to intermediate CYP2D6 metabolisers experience more adverse reactions associated with SSRI's that are dependent upon CYP2D6 for their metabolism [4]. Studies have also shown that ultra-rapid metabolisers experience a decrease in drug efficacy, however, a prospective study has shown no association between metaboliser status and drug efficacy [4]. According to our findings evidence is conflicting regarding the clinical importance of pharmacogenetic testing and SSRI response and associated adverse effects.

As previously stated, the Amplichip CYP450 pharmacogenetic test is available to determine the metabolising status of individuals, and has the potential to be used to assist physicians when prescribing a variety of medications, including SSRI's. GeneSightRx Psychotropic is another commercially available pharmacogenetic test that tests via buccal swab for CYP450 polymorphisms [11].

Although there are multiple tests that are available for detecting these genomes in patients on SSRI therapy, the FDA has no specific recommendations for testing prior to therapy and their therapeutic, genotype-specific treatment has not been documented at this time. Although routine pharmacogenetic testing is currently not recommended for individuals taking an SSRI, studies have shown that there are some clinical applications that can be taken into consideration when prescribing these medications for individuals who have been tested. Further studies are being conducted with the intention to further define the relevance of testing in these particular patients [4].

Abacavir

Abacavir is an oral nucleoside reverse transcriptase inhibitor that is indicated for treatment of human immunodeficiency virus type-1 (HIV-1) infection. Although this drug is widely prescribed, it is associated with severe and even fatal hypersensitivity reactions, to which it has been assigned a Black Box Warning [12]. Hypersensitivity reactions occur in about 5% of individuals who become exposed to abacavir. This reaction may involve 2 or more of the following: fever, skin rash, malaise/fatigue, gastrointestinal symptoms and/or respiratory symptoms [12]. If dosing of abacavir is continued, the symptoms of the hypersensitivity reaction become more severe overtime and if an individual is suspected to have this reaction, abacavir treatment should be discontinued immediately.

The biomarker of interest pertaining to abacavir's hypersensitivity reaction is the major histocompatibility complex allele HLA-B*5701. Several retrospective analyses have identified a strong association between the hypersensitivity reaction and this specific biomarker [13]. According to, PREDICT-1, a double blinded, randomized, prospective study, screening for the presence of the HLA-B*5701 allele prior to initiating abacavir therapy eliminated the occurrence of immunologically confirmed hypersensitivity reactions [14]. In patients who were identified as clinically suspected to have a hypersensitivity reaction, 3.4% occurred in pre-screened patients as compared to 7.8% in those who were not screened. This study also concluded that by pre-screening with a pharmacogenetic test, medication related adverse reactions can be prevented [14]. As of July, 18th, 2008, the FDA approved changes to the package insert of abacavir to include information regarding the relationship between the HLA-B*5701 and the abacavir hypersensitivity reaction. The package insert states "Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir. Prior to initiating therapy with abacavir, screening for the HLA-B*5701 allele is recommended" [5]. Current pharmacogenetic tests for the presence of the HLA-B*5701 allele can be performed via buccal swab or blood test [5]. Figure 3 illustrates a proposed treatment algorithm based upon HLA-B genotype to be used prior to initiating therapy with abacavir in individuals who are abacavir treatment naïve [15].

Tamoxifen

Tamoxifen is a weak estrogen receptor antagonist that is converted to the metabolite endoxifen (4-hydroxy-N-desmethyl-tamoxifen). Endoxifen has much higher potency and a 6-10 fold higher serum concentration than tamoxifen [16]. It is used to treat metastatic breast cancer, prevent the recurrence of estrogen-receptor-positive breast cancer, and to prevent cancer in high risk populations [4]. CYP2D6 is required to metabolise tamoxifen into endoxifen and there is a correlation with the CYP2D6 genotype and endoxifen plasma concentrations. Studies show that variants in this genotype are associated with reduced or no enzyme activity, as well as exaggerated enzyme activity in those with more than two normally functioning alleles, potentially predicting response to tamoxifen. It is also noted that concomitant use of drugs that inhibit CYP2D6 may reduce the action of tamoxifen [4]. In a retrospective sub study of patients enrolled in the prospective randomized clinical trial ATAC, Rae et al. studied the effect of variant CYP2D6 genotypes and their correlation to breast cancer patients being treated with tamoxifen [16]. They found that there was no statistically significant association between CYP2D6 variants and breast cancer outcomes or rates of recurrence. In a similar study, the BIG1-98 done by the Breast International Group, similar results were obtained from patients on adjuvant tamoxifen therapy and their recommendation is that genotyping is not recommended for these patients and that the avoidance of CYP2D6 inhibitors while on tamoxifen is not necessary [4]. The FDA has not made any solid recommendations about testing for the CYP2D6 genotype before prescribing tamoxifen, due to the fact that there is no sufficient evidence of the benefit. Although the evidence surrounding genetic testing in individuals on tamoxifen therapy is conflicting, clinicians should be aware that there is the potential for tamoxifen's efficacy to be reduced in patients also taking CYP2D6 inhibitors [4].

Tramadol

Tramadol is an analgesic medication that is prescribed to treat moderate pain. Tramadol is a pro drug that is metabolised to (-)S,S-O-desmethyltramadol and (+)R,R-O-desmethyltramadol enantiomers. The (+)R,R-O-desmethyltramadol enantiomer has a high affinity for the μ-opioid receptor. The formation of this active metabolite is catalysed by CYP2D6 [17]. In clinical studies, it is shown that poor metabolisers of CYP2D6 do not respond, or respond very poorly to tramadol's analgesic effects. On the other hand, those with ultra-rapid and extensive CYP2D6-mediated metabolism have the potential of developing high concentrations of the active metabolite and could be at a risk for exaggerated effects or intoxication [17]. A study conducted by Kirchheiner et al. showed that the ultra-rapid metabolisers, patients with a CYP2D6 duplication allele, had a significantly higher plasma concentration of the active metabolite compared to the extensive metabolisers, those with 2 active CYP2D6 genes [17]. The ultra-rapid metabolisers also had an increased pain threshold and pain tolerance. They concluded that although the differences in effect were small, ultra-rapid metabolisers were more sensitive to tramadol, putting them at a greater risk of adverse events. In another study conducted by Enggaard et al., they compared the effect and serum concentrations of IV tramadol for acute pain in both extensive and poor metabolizers of CYP2D6 [18]. They found a significant difference in serum concentrations of both enantiomers amongst the two groups, with the concentrations being significantly larger in the extensive metabolisers group. They concluded that poor metabolisers of CYP2D6 may not receive adequate pain relief from tramadol therapy. Currently, the FDA has this pharmacogenetic biomarker included in the label for tramadol, but testing is not recommended [3].

Ethical Considerations

Recent developments in the area of pharmacogenetics have raised some ethical issues that are receiving widespread consideration. Some of the ethical concerns discussed in literature include: the

sharing and storage of genetic information, changes in physician-patient relationships, regulatory issues, and discrimination and stigmatization of groups and individuals. Some pharmacogenetics tests carry the possibility of revealing additional sensitive information about the patient. A confidentiality concern arises because genetic information is not only personal, but familial at the same time. Using pharmacogenetic testing to help understand the association of genetics and drug response, individuals from particular ethnic communities and well as people with certain disease states could be potentially be open to discrimination or stigmatization. The retention of DNA samples poses the problem that the individual's genetic information would be stored in computerized databases and could be vulnerable to a violation of privacy. This could potentially lead to discrimination by employers and insurance companies in the event that this information was accessed inappropriately. Pharmacogenetics is also likely to create a more complex doctor-patient encounter. There will be an increased need for genetic knowledge throughout all levels of medical services. All health care providers involved need to be well educated on the subject, therefore, it is imperative to develop ways to incorporate the subject into the educational curriculum. Due to the potential ethical concerns pharmacogenetics poses, it will be important to develop appropriate policies and guidelines for its use [19].

Although the implementation of pharmacogenetics into routine practice is not occurring at the rate it was expected to, it is a maturing field that is being integrated into the practice of medicine more each day [2]. The future of pharmacogenetics and its place in clinical practice is still unclear, but there is the potential for individuals to be broadly genotyped and that their genetic information will guide therapy decisions throughout their lifetime [20]. This could potentially lead to clinicians being able to choose the best drug and dose that will result in better outcomes for patients, with the least chance for harm based on genotype [20].

Limitations

When performing the literature search, only articles published after the year 2004 were included. Of the articles included, there was a lack of the gold standard trials, prospective, and randomized-controlled trials. The practice of pharmacogenetics would benefit not only from these trials, but also more specific trials comparing different dosages. For example, a person who is identified as an ultra-rapid metaboliser may require a higher dosage as compared to that of a poor metaboliser, to achieve the same pharmacological outcome. If this can be concluded from a study it will give specific dosage guidelines based on genotypes [6]. A limitation and reason for so few prospective, randomized control trials is they may be considered unethical, especially when looking for an association between severe adverse effects in different genotypes [21]. Another limitation is the clinical validity of the pharmacogenomic test to detect a specific disorder caused by genotypes. According to Scott, most pharmacogenomic assays have a low positive predictive value [21]. The same type of pharmacogenomic test was not used for all of the studies reviewed. Another important limitation is some of the included studies did not utilise a large enough study population in order to provide significant conclusions. Along with this, some of the included studies needed a more racially diverse population. A lack of cost benefit analysis studies has limited healthcare payers to the evidence of the benefits of pharmacogenomic testing. With more of these studies, they may be more inclined to pay for such testing, therefore, decreasing the barrier to access for some patients. Finally, some of the included studies were exposed to recall bias. In the case of warfarin, for example, patients were relied on to inform investigators of things such as, medication compliance and vitamin K intake for the week.

Conclusion

Pharmacogenetics is an emerging field that investigates variations in candidate genes that are relevant to drug metabolism, and are based on phenotype observations. The identification of these polymorphisms is leading to an increased understanding of variability in pharmacodynamic and pharmacokinetic responses between individuals and potentially opening doors to improved medication efficacy, a reduction in adverse events, and more individualized care. Currently, pharmacogenetic testing has not been fully implemented into clinical practice. There remains a need for additional prospective, randomized, control trials including larger and more racially diverse populations, in order to provide a more complete understanding of how pharmacogenetic information may be applied to clinical situations. As more information becomes available, healthcare providers will also need additional education and training pertaining to the use of pharmacogenetic testing and its potential clinical benefits. At this time, pharmacogenetic testing is relevant in clinical practice in select patient specific situations. The future of pharmacogenetic testing has a great potential to provide healthcare providers with the additional information needed to provide optimal individualized care and its utility is expected to increase as more high level evidence becomes available.

Acknowledgement

No funding was received for the realisation of this manuscript.

Disclosure

The authors of this manuscript have no conflicts of interest to report.

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