



Applicability of Pharmacogenetic Drug-Gene Pair Strategy in Clinical Studies: Regulatory Considerations in Latin America

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Abstract

Pharmacogenetics, one of the corner stones of personalized medicine, has the potential to change the way in which health care is offered by stratifying patients into various pretreatment categories, such as likely responders, likely non-responders or likely to experience adverse drug reactions. In order to advance, Pharmacogenomics has been utilized as tool to improve a drug's benefit/risk ratio and the efficiency of drug development. This article shows the importance of the applicability of drug-gene pair in the clinical practice and the regulatory considerations about pharmacogenomics. Pharmacogenomic allows individualize therapy with the intent of maximizing effectiveness and minimizing risk. Thus, it is important to regulate this subject in order to make decisions based on risk-benefit criteria, allowing the rational use of drugs. The integration of genomic biomarkers in clinical trials and other studies, as well as the used technology, should follow certain principles in order to generate reliable evidence for decision-making and patient treatment.

Keywords: Polymorphisms; Pharmacogenetics; Pharmacogenomics; CYP; Clinical studies.

Introduction

Pharmacogenetics and Pharmacogenomics areas are currently emerging fields focused to manage pharmacotherapy that may prevent under treatment while avoiding associated drug toxicity in patients. It is known that pharmacokinetic factors affecting absorption, distribution, biotransformation and excretion influence the plasma and tissue concentration reached by drugs. Therefore, polymorphism of genes encoding drug transporters, biotransformation enzymes and drug targets will influence drug efficacy and safety [1]. Despite the enormous amount of known information about the genetic basis of variable response to drugs, it has little influence on its application to the current clinical practice. Thus, acceptance of pharmacogenomic studies in medical practice is gradual. Several issues have prevented its rapid implementation, such as, a) lack of readily available clinical laboratories which can perform these tests quickly and cost-effectively, b) shortage of health care professionals who can interpret the test data and associated clinical pharmacology and c) doubts whether insurance companies will pay for the study. In addition, many ethical questions pose continuing challenges. However, the number of drugs approved with a reference to the genetic study in labeling information is increasing [2, 3].

Relevance for Clinical Implementation

Of course pharmacogenomics has several limitations to its application in clinical practice which should be addressed; some of them have been analyzed by Agúndez et al. [4]. These limitations include the lack of sufficient evidence for cost-efficiency, the need for the identification of new biomarkers for drug toxicity and response, technical limitations and ethnicity questions. Together, we know that inter-individual variability to drug response exists, even in individuals with identical pharmacogenomic profile, giving rise to the idea that pharmacogenomics is only one of the several factors to be considered in dose adjustment. Therefore algorithms including anthropometric, lifestyle and environmental factors appear to be the best approach. Therefore, polymorphism of genes encoding drug transporters, biotransformation enzymes and drug targets will influence drug efficacy and safety [4].

Another restriction for the use of pharmacogenomics is the poor information about pharmacogenes in Latin America populations, which prevents direct extrapolation of the dosage of drugs with clinical studies performed in other ethnic groups. Since profound variation in the effect of drugs has been described to be associated to the genetic polymorphisms in diverse populations, ethnicity appears to be an important issue in Latin America [5]. In this sense, in order to have a first approach, particularly in American Hispanic populations, we have previously discussed the implications of interethnic and intra-ethnic genetic variability. In this respect, it is clear that there is a need for developing more and well-designed studies in Latin American populations to better address the issue that the introduction of pharmacogenomics in clinical practice. These studies should include ethnic comparison of pharmacogenomic profiles, the impact of polymorphism on phenotype, gene expression and regulation, metabolic

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profiles of patients with a given drug and relevant environmental factors that influence drug response [4].

Of course, before use in the clinical routine selected pharmacogenes must demonstrate, in retrospective and prospective studies, a sufficient value to have good cost-effectiveness. Pharmacology of the future intends to conduct individualized pharmacotherapeutic treatment for the manifestation of a disease and the appropriate dose for the therapeutic effect in a given patient, minimizing the risk of adverse reactions [6, 7]. Therefore the main idea is the accomplishment of the five “R” for drug therapy “the Right dose of the Right drug for the Right indication in the Right patient at the Right time”. For instance, nowadays the individualized treatments are a pressing need. The current formula of standard pharmacotherapy is not ideal according to the great variability among patients [8].

The rapidly evolving field of pharmacogenetics holds great promise for assisting the selection of patient-individualized treatment regimens and dosages. A vast number of single nucleotide polymorphisms have been discovered in genes thought to be involved in the regulation of drug metabolism; however, relatively few studies have been conducted that establish a link between genotype, efficacy and safety of drugs [9].

In short, integration of pharmacogenomics in clinical practice needs training of healthcare professionals and citizens, moreover legal and regulatory guidelines and safeguards will be required. The answers to the question of which patient should receive which drug and dose will be not easy, but we believe that the approach offered by pharmacogenomics should be incorporated into the decision making process. A more rational use of expensive treatment drugs together with actions to minimize patient toxic events and its consequences, would dramatically reduce medical costs, as an added [10, 11].

The ultimate goal of pharmacogenetic research is to predict individual's responses to drug therapy and subsequently to adapt the therapeutic strategy. In this regard, it is estimated that gene polymorphisms account for 20 to 95% of the variability in therapeutic response and toxicity. Of all the known drugs involved in adverse reactions about 80% are metabolized by polymorphic enzymes.

Regulatory Framework

The main mission of any regulatory agency is to control the quality, safety and efficacy of drugs. The main regulatory agencies around the world: Food and Drug Administration (FDA) from United States of America, Health Canada (Canada), European Medicines Agency (EMA) from Europe and Pharmaceuticals and Medical Devices Agency (PMDA) from Japan have issued guidance's about pharmacogenomics as well as the International Conference on Harmonization (ICH) which is integrated by FDA, EMA, PMDA and Pharmaceutical companies [12-15].

There are different regulatory dispositions related with pharmacogenomic studies; for example: concept paper, reflection paper, drafts, position paper, which explains how to implement the regulations and guidance about pharmacogenomic assays.

EMA is the regulatory agency with more regulations about this topic, followed by FDA and International Conference of Harmonization (ICH). These documents explain about the reception, codification and storage of samples as well as the use of biomarkers, and ethical issues. Recently, EMA published a new guide in relation with good practices for pharmacogenomic which comprises requirements related to the choice of appropriate genomic methodologies during the development and the life-cycle of a drug [16, 17].

Several pharmacogenomics tests have been approved by regulatory agencies that are either designed for a specific drug like TPMT/thioguanine, TPMT/azatjipirine, CYP2C9/warfarin, CYP2D6/amitriptyline, and UGT1A1/irinotecan [18].

An important regulatory feature is ‘biomarker qualification’. A PGX biomarker to be used in drug developments should be qualified and accepted by a regulatory agency because use of an unqualified and unacceptable biomarker may result in misinterpretation of the acquired data due to false signals (false-positive or -negative signal) and, therefore, may not be used in regulatory decision-making. Biomarker qualification by a regulatory agency is an important process to qualify the objective and context of use of the biomarker before it can be widely used in drug development. To confirm the acceptability of the biomarker, each agency-PMDA, the FDA and the EMA has established a biomarker qualification process. Thus, in many cases the identified biomarkers are used for more than one drug and consequently the same biomarker can be used for different [19].

Ethical Issues

This is a big challenge for pharmacogenomics, particularly as science and technology continue to advance very rapidly. E.18 ICH Guideline explains this important topic, concerning to informed consent, transparency and communication findings.

Whole genome sequencing, for example, is poised to eliminate the need for individual genetic tests, thus raising ethical concerns about the creation of genetic information which individuals may or may not want to know and which may or may not remain privately secured. Ethical Committee has a great responsibility, should approve the pharmacogenomic studies taking into account, Balancing risk-benefit, Ethical responsibilities of all the participants in the study, The patients need all necessary information to make the own decision. All anticipatable information of expected benefits or expected harms. Concern of individual participants regarding anonymity, privacy and confidentiality should be respected and should be addressed in a research agreement the discrimination should not be allowed and the protocol should always refer the alternative treatment in case the patient according the result cannot take the drug. Ethics should be reinforced and must consider three critical points in their design and implementation: management of risks, informed consent and privacy and confidentiality [20, 21].

Regulatory restrictions for Latin America

Latin America has a population very heterogeneous, the medical services are not equitable, the manufacturing of drugs is for specific group of population and another important aspect is that Latin America import drugs and posology. It means the population consumes drugs with clinical trials carried out mainly in USA and Europe.

Some of the possible solutions are: to develop global development program in several countries rather use bridging studies, to prepare the health professional involved in this topic. Particular attention should be addresses for special populations, like children and geriatrics patients and to design clinical trials with Latin America populations [22].

Main regulatory challenges

- Education and training of all the health professionals involved (researchers, medical doctor, regulators etc.).
- Lack of validation of test procedures.

- Lack of prospective studies to validate recommendations.
- Cases of failure of efficacy or development of toxicity rarely characterized in pharmacogenetic terms.
- Qualification of biomarkers.

Future dynamics of drug labels

The Summary of product characteristics (SMPC) or the label sets out key elements of drug benefits and risks relevant to the clinical use of the product defined during the medicine regulatory assessment process. At present, the SMPCs of about 150 drugs approved by the European Commission (EC) mainly used in oncology include pharmacogenomic information and for the US FDA, a similar number of drug labels apply. Moreover, pharmacogenomic labels are of particular

importance for treatments where the therapeutic index is narrow and it's where a small overdosing poses a substantially increased risk for adverse drug reactions.

The healthcare professionals (prescribers, insurers and regulators) will want to know if there is a substantial impact of pharmacogenomics on the safety and efficacy of the drug on an individual [23]. Almost 15% of EMA-evaluated medicines contain pharmacogenomics information in their label that directly impacts patient treatment. Some sections include dosage and administration, drug interactions and overdose, etc. In Table 1 it is shown types of pharmacogenomics information for labeling [24] of course, before use in the clinical routine selected pharmacogenes must demonstrate, in retrospective and prospective studies, a sufficient value to have good cost-effectiveness.

Table 1: Types of pharmacogenomic information for labeling [24]

Section of Label	Pharmacogenomic information
Therapeutic indications	If the product's indication depends on a Particular genotype or the expression of a gene or a particular phenotype, then this should be stated in the indication.
Dosage and administration	Where necessary, dosage adjustments in Patients with a particular genotype should be stated (with cross-reference to other relevant sections for further detail as appropriate).
Contraindications	Linked to a particular genotype.
Special warning and precautions	Subjects or patients with a specific genotype or phenotype might either not respond to the treatment or be at risk of a pronounced Pharmacodynamic effect or adverse reaction. These may arise because of non-functioning enzyme alleles, alternative metabolic pathways (governed by specific alleles) or transporter deficiencies. Such situations should be clearly described if known.
Drug Interactions	If interactions with other medicinal products depend on polymorphisms of metabolizing enzymes or certain genotypes, then this should be stated.
Undesirable effects	This section may include information on any clinically relevant differences specifically observed in patients with a specific genotype.
Overdose	If applicable, counteractive measures based on genetic factors should be described.
Pharmacodynamic properties	Any relevant pharmacogenetics information from clinical studies may be mentioned here. This should include any data showing a difference in benefit or risk, depending on a particular genotype or phenotype.
Pharmacokinetic properties	Variations with respect to polymorphic metabolism should be described, if clinically relevant, in quantitative terms.

Pharmacology of the future intends to conduct individualized pharmaco-therapeutic treatment for the manifestation of a disease and the appropriate dose for the therapeutic effect in a given patient, minimizing the risk of adverse reactions. Therefore the main idea is the accomplishment of the five “R” for drug therapy “the Right dose of the Right drug for the Right indication in the Right patient at the Right time”. For instance, nowadays the individualized treatments are a pressing need. The current formula of standard pharmacotherapy is not ideal according to the great variability among patients [25].

The rapidly evolving field of pharmacogenetics holds great promise for assisting the selection of patient-individualized treatment regimens and dosages. A vast number of single nucleotide polymorphisms have been discovered in genes thought to be involved in the regulation of drug metabolism; however, relatively few studies have been conducted that establish a link between genotype, efficacy and safety of drugs.

Another important feature is the importance of pharmacogenomic in the rescue of drug from the market serious adverse drug reactions represent one of the main causes of death in USA and other countries for postmarketing drug withdrawal and represent billions of US dollars in costs every year in all developed countries. Some of these serious adverse drug reactions might be avoided by systematically screening for pharmacogenomics risk factors [26].

Conclusion

In short, integration of pharmacogenomics in clinical practice needs training of healthcare professionals and citizens, moreover legal and regulatory guidelines and safeguards will be required. The answers to the question of which patient should receive which drug and dose will be not easy, but we believe that the approach offered by pharmacogenomics should be incorporated into the decision making process. A more rational use of expensive treatment drugs together with actions to minimize patient toxic events and its consequences, would dramatically reduce medical costs, as an added benefit.

The most relevant group of barriers was related to the need for clear guidelines for the use of pharmacogenomics in clinical practice, followed by insufficient awareness about pharmacogenomics among clinicians and the absence of regulatory institutions that facilitate the use of pharmacogenetic tests will be presented.

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