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Review

Points-to-consider documents: Scientific information on the evaluation of genetic polymorphisms during non-clinical studies and phase I clinical trials in the Japanese population☆

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ABSTRACT

Pharmacotherapy shows striking individual differences in pharmacokinetics and pharmacodynamics, involving drug efficacy and adverse reactions. Recent genetic research has revealed that genetic polymorphisms are important intrinsic factors for these inter-individual differences. This pharmacogenomic information could help develop safer and more effective precision pharmacotherapies and thus, regulatory guidance/guidelines were developed in this area, especially in the EU and US. The Project for the Promotion of Progressive Medicine, Medical Devices, and Regenerative Medicine by the Ministry of Health, Labour and Welfare, performed by Tohoku University, reported scientific information on the evaluation of genetic polymorphisms, mainly on drug metabolizing enzymes and transporters, during non-clinical studies and phase I clinical trials in Japanese subjects/patients. We anticipate that this paper will be helpful in drug development for the regulatory usage of pharmacogenomic information, most notably pharmacokinetics.

1. Background

The Project for the Promotion of Progressive Medicine, Medical Devices, and Regenerative Medicine by the Ministry of Health, Labour and Welfare was established in 2012. One of the projects that was adopted, "evaluation procedures for the efficacy and safety of pharmaceuticals that use pharmacogenomics," conducted a non-clinical study and early-phase clinical trials on investigational drugs, and evaluated the effects of genetic polymorphisms of drug-metabolizing enzymes and transporters primarily involved in those trials. This work was conducted at the Graduate School of Pharmaceutical Sciences and Faculty of Pharmaceutical Sciences, Tohoku University, in cooperation with the National Institute of Health Sciences and Pharmaceuticals and Medical Devices Agency.

As a main achievement of this project, we compiled the current scientific information on genetic polymorphisms, which had been evaluated during these non-clinical studies and phase I clinical drug trials in Japanese subjects/patients, obtained through this project and scientific papers. This report focuses on the genetic polymorphisms of drug metabolizing enzymes (cytochrome P450 enzymes among others) and transporters with reported functional significance and allele frequencies of 1% or higher in the Japanese population, and outlines *in vitro* procedures for the evaluation of their functional effects on investigational drugs. This report also provides examples of genetic polymorphisms and somatic mutations of proteins involving drug efficacy or adverse drug reactions. We believe that this information will be helpful to accelerate future research and continued discussions on drug development using

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pharmacogenomic information (e.g., dose adjustment and avoidance of adverse reactions) in Japan and possibly other East Asian countries. Furthermore, a guideline from European Medicines Agency describes that 1) a relevant involvement of a known polymorphic enzyme cannot be excluded (i.e., non-clinical *in vitro* data predict >50% to be cleared by a single polymorphic enzyme *in vivo*), it is advised to genotype the first time substance exposure in phase I clinical trial, 2) if phase I studies indicate that pharmacogenetics influences the pharmacokinetics of a drug to a possible clinically relevant extent (i.e., >25% of the drug is metabolized by a single polymorphic enzyme), this should be reflected in the design of the Phase II studies. No such a guideline is there in Japan. Since multi-regional clinical trials including Japan have been common nowadays, clear information on frequent and functional genetic polymorphisms in Japanese population should be useful to promote the safer attendance of Japanese patients into the trials (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/02/WC500121954.pdf). The Graduate School of Pharmaceutical Sciences and Faculty of Pharmaceutical Sciences, Tohoku University anticipated that this information will serve as a scientific basis for discussion to make regulatory guidelines in the future.

2. Introduction

2.1. Purpose

Individual differences in efficacy and safety of drugs are well known, and factors affecting these differences can be classified into intrinsic and extrinsic factors. As listed in the ICH-E5 guideline, extrinsic factors include climate, culture, degree of drug compliance, and method of conducting or endpoint of the clinical trial, while intrinsic factors include gender, body weight and height, and polymorphisms of genes involved in drug metabolism. In recent years, many studies on genetic polymorphisms in drug-metabolizing enzymes and transporters have demonstrated associations with drug efficacy and/or adverse drug reactions [1–3]. The use of genetic information could lead to increased efficacy and decreased adverse reactions.

Drug efficacy can be efficiently demonstrated in clinical trials by excluding specific patient groups with certain types of genetic backgrounds that are associated with no or very low efficacy of the drug. For example, some studies showed a linkage between reduced drug efficacy and decreased activity of metabolizing enzymes due to genetic polymorphisms [4,5]. As another example, drug toxicity can be caused by an elevation in blood/tissue concentrations by a reduction in drug metabolizing enzyme or transporter activities by genetic polymorphisms, leading to decreased excretion or decreased elimination of reactive metabolites [6]. Therefore, the use of information on genetic polymorphisms related to pharmacokinetics/drug efficacy/adverse drug reactions could potentially prevent delays in drug development and reduce costs associated with the onset of serious adverse reactions.

This report aims to present scientific information for evaluation of genetic polymorphisms (mainly on drug-metabolizing enzymes and transporters) and their functional effects that can be taken into consideration during non-clinical studies (*in vitro* studies using human samples) and phase I clinical trials in the Japanese population.

2.2. Scope of application

This report will present the methodology and important considerations for referral when pharmaceutical companies obtain information on genetic polymorphisms and/or assess their functional significance for investigational drugs in non-clinical studies. These evaluations will be helpful to design phase I clinical trials in the Japanese population. The scope of this document is limited to exploratory evaluations of the effects of genetic polymorphisms. The methodologies and information presented here are based solely on current knowledge, and thus, future strategies for drug development should not be limited to this document.

3. Analysis methods and examples of target genes

3.1. Analytical methods for genetic polymorphisms

Analytical methods for genetic polymorphisms can be divided into 1) candidate gene analysis and 2) comprehensive gene analysis. This section briefly outlines the advantages and disadvantages of the two methods.

3.1.1. Analysis of genetic polymorphisms of candidate genes

Enzymes that contribute to investigational drug metabolism can be identified by non-clinical studies using human hepatocytes, their microsomal, cytosolic, or S9 fractions, or expression systems of each drug-metabolizing enzyme. Cytochrome P450 and glucuronyl transferase are present in these samples (except for the cytosolic fraction). In addition, a growing number of studies have revealed the involvement of drug transporters that contribute to the uptake/excretion of drugs into/from the small intestine, liver, kidney, and other organs. When known drug metabolizing enzymes/transporters are involved in pharmacokinetics, efficacy, and the safety of the drug, it is possible to explore novel, related genetic polymorphisms and to evaluate the effects of the polymorphisms on the metabolism of the investigational drug in non-clinical studies; this will allow the importance of these polymorphisms to be considered in subsequent clinical phase I trials. Genetic polymorphisms associated with functional changes have previously been reported, especially for major cytochrome P450s, several conjugating enzymes, and transporters. We can use this information when selecting genes and their polymorphisms for analysis.

For candidate gene analysis, we can use several methods, including conventional sequencing (Sanger method) and novel sequencing methods using highly-efficient sequencers (next generation). For analysis of known genetic polymorphisms, a number of methods can be used, including the PCR-restriction fragment length polymorphism (RFLP) method, the allele-specific PCR method, DNA microarrays (products specialized for pharmacokinetics-related genes), and other sequencing/PCR/hybridization-based methods [7,8]. These methods can be selected based on factors such as the number of samples, adjacent sequences of genetic polymorphisms, instrument availability, and measurement duration.

Advantages of candidate gene analysis generally include its relatively low cost, low multiplicity corrections in statistics since it measures limited numbers of polymorphisms, and the need for a relatively small number of patients. A disadvantage of this method is that it cannot find associated polymorphisms when unknown molecules are involved in drug responsiveness. Blood or a buccal swab could be used as a source of DNA, for example.

3.1.2. Comprehensive analysis of genetic polymorphisms

Genetic polymorphisms that are involved in drug responsiveness can sometimes be difficult to determine, such as when unknown drug-metabolizing enzymes and transporters contribute to pharmacokinetics, efficacy, and adverse drug reactions. In these cases, it is necessity to search for related genetic polymorphisms by sequencing exon and/or transcriptional regulatory regions of several candidate genes or even performing genome-wide association studies (GWAS) for a large number of genetic polymorphisms.