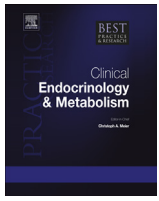
Best Practice & Research Clinical Endocrinology & Metabolism 28 (2014) 783–793

Contents lists available at ScienceDirect

Best Practice & Research Clinical Endocrinology & Metabolism

journal homepage: www.elsevier.com/locate/beem



2

Pharmacogenetics of osteoporosis

Francesca Marini, PhD, Research Fellow, Molecular Biologist [1],
Maria Luisa Brandi, MD, PhD, Full Professor of Endocrinology [*]

Metabolic Bone Unit, Department of Surgery and Translational Medicine, University of Florence, Florence, Italy

Keywords:
pharmacogenetics
gene polymorphism
osteoporosis
anti-fracturative drugs
drug response

The challenge of personalized medicine is to move away from the traditional 'one-size-fits-all' pharmacology to genotype-based individualized therapies. As an individual's response to drugs is under the control of genes, personal genetic profiles could help clinicians to predict individual drug response and prescribe the right drug and dose, thereby optimising efficacy and avoiding risk of adverse effects. Currently, the concrete application of pharmacogenetics into clinical practice is limited to a few drugs, and the genetic prediction of drug response is far from clear for many of thve principal complex disorders. This is even more evident in the field of osteoporosis and metabolic bone disorders, for which few pharmacogenetic studies have been conducted, and no conclusive results are available. In this chapter, we review recent research on pharmacogenetics of osteoporosis, evaluate criticisms, and offer possible suggestions for improvements in this field and for possible future applications into clinical practice.

Introduction

The rise in life expectancy has strongly increased the incidence of chronic and degenerative complex diseases. These disorders require long-term pharmacological treatments; therefore, it is important that prescribed drugs are effective and do not induce severe adverse events so that people taking prescribed medication are granted a better quality of life, and drug-related morbidity, mortality, and costs of drug-induced hospitalization are reduced.

* Corresponding author. Metabolic Bone Unit, Department of Surgery and Translational Medicine, University of Florence, Largo Palagi, 1, 50139 Florence, Italy. Tel.: +39 055 7946304; Fax: +39 055 7946302.
E-mail addresses: f.marini@dmi.unifi.it (F. Marini), marialuisa.brandi@unifi.it (M.L. Brandi).
[1] Metabolic Bone Unit, Department of Surgery and Translational Medicine, University of Florence, Viale Pieraccini, 6, 50139 Florence, Italy. Tel.: +39 055 4271507; Fax: +39 0554271506.

http://dx.doi.org/10.1016/j.beem.2014.07.004
1521-690X/

For many common multifactorial disorders, various drugs with different molecular mechanisms of action are available. This offers clinicians the opportunity to select the most effective drug for any single patient based on personal variables that can control drug response (e.g. gender, age, ethnicity, clinical family history, renal, hepatic function, or both, concomitant pathologies and medications, diet, alcohol intake, and smoking). For most of the currently available drugs, real effectiveness, and the possible development of secondary adverse effects, cannot be predicted before drug administration. Indeed, today, most therapeutic plans are generally standardized, and they can be modified for each patient only after ascertaining their clinical response to drug administration.

The challenge of personalized medicine is to move away from the traditional 'one-size-fits-all' pharmacology to genotype-based individualized therapies. Personalized medicine assumes that drug response is related to personal features (e.g. sex, age, ethnicity, renal, hepatic function, or both), environmental influences (e.g. diet, concomitant therapies, alcohol assumption, smoke), and mainly to changes in drug pharmacokinetics and pharmacodynamics, which are dependent on an individual's genome and epigenome.

Pharmacokinetics and pharmacodynamics regulate the availability, activity and metabolism of drugs within the organism, and are responsible for personal drug response, and are both under the control of genes. Therefore, a person's genotype is strongly responsible for their response to drugs, both in terms of efficacy and safety. Genetic deficiencies (or over-activity of one or more drug-metabolising enzymes), and genetic alterations in drug absorption and distribution proteins, can strongly influence elimination and accumulation profiles of a drug, or both. They can also influence the availability of a drug to its specific tissue and cell target, as this is responsible for an individual's response to drugs. This dictates the need for personal selection of drug type, dose, or both, based on a person's personal characteristics and variables, and also on their specific genotype. Pharmacogenetics and pharmacogenomics aim to individuate the gene variations responsible for the regulation of pharmacokinetics, pharmacodynamics and mechanisms of action of drugs; the main goal of these novel disciplines is to predict the response to drugs before their administration based on a patient's genotype [1].

In the future, the expectation is that patients could present a chip containing their personal genetic profiles, thus, enabling clinicians to prescribe the right drug at the right dose, and to optimize clinical efficacy and avoid any risk of adverse effects.

The role of genetic markers in predicting drug response is currently unclear. A number of pharmacogenetic tests have been approved by regulatory agencies, are commercially available, and are used in clinical practice.

A Table of 'Pharmacogenomic Biomarkers in Drug Labels' is freely available on the Food and Drug Administration (FDA) website at http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm. In June 2007, The US Food and Drug Administration also released general guidance on performing and handling pharmacogenetics tests for application in clinical practice http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm077862.htm.

Of all the commercial drugs in the European Union, only about 20% are labelled by genomic information for personalized use. In November 2011, The European Medicine Agency (EMEA) released guidance on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products (available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/02/WC500121954.pdf). The guideline addresses the influence of pharmacogenetics on drug pharmacokinetics, encompassing considerations and requirements for the design and conduct of investigations during drug development.

The Pharmaceutical Medicines and Devices Agency (PMDA) in Japan approved the label of about 14% of all drugs with pharmacogenetic information. Most drugs included in the pharmacogenetic lists of FDA, EMEA and PMDA are represented by drug-metabolising enzymes, but none of them are administered in the pharmacotherapy of osteoporosis or other metabolic bone disorders.

Pharmacotherapy of osteoporosis

Bone is an active and dynamic tissue, characterized by a lifetime-spanning complex process of renewal and remodelling. Bone remodelling is a fine process, consisting of an osteoclast resorption