Pharmacogenetics and pharmacogenomics: are they still promising?

A. Pirazzoli∗, G. Recchia
GlaxoSmithKline Spa, Via Alessandro Fleming 2, 37135 Verona, Italy
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Abstract

In the last several years pharmacogenetics and pharmacogenomics have attracted the interest of the scientific community and of important pharmaceutical groups.

What is the consequence for medicine and for the pharmaceutical industry? What has emerged from this investment, and what can we expect for the future?

As with many new technologies, pharmacogenetics and pharmacogenomics were first adapted with much enthusiasm, and then found to require time and experience, together with sustained investment, before they could take their full place in drug discovery and development. The benefits of these technologies are now emerging, however, and they have become essential tools for the pharmaceutical industry.

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1. Distinguishing pharmacogenetics from pharmacogenomics

There is at present no consensus in the literature on the definition of pharmacogenetics and pharmacogenomics, and actually the two terms are often used interchangeably.

However, in this paper the definition provided by the “Position paper on terminology in pharmacogenetics”, issued by the European Agency for the Evaluation of Medicinal Products (EMEA) and very recently adopted by the Committee for Proprietary Medicinal Products (CPMP) will be used [1]. According to this paper, “pharmacogenetics is the study of interindividual variations in DNA sequence related to drug response”, while “pharmacogenomics is the study of the variability of the expression of individual genes relevant to disease susceptibility as well as drug response at cellular, tissue, individual or population level. The term is broadly applicable to drug design, discovery and clinical development”.

2. Pharmacogenetics and its delivery

Pharmacogenetics is expected to deliver targeted treatments and hence more effective and well-tolerated drugs.

The promise of pharmacogenetics is to identify the genetics factors underlying the differences observed in individual response to drugs, the so called medicine response profile, and hence develop pharmacogenetic tests. When applied in medical practice, these tests, by predicting individual response, can guide prescription to maximise benefits and minimise risks for the patient. The potential of this strategy is enormous. Besides the obvious benefits for patients and doctors, improved cost effectiveness could be realised as a consequence of this optimisation in the use of drugs. Particularly, the possibility of reducing side effects and the deriving costs seems extremely promising.

The medical, social and economic aspects associated with adverse drug reaction have been highlighted by many studies [2–4]. More recently, a study has provided a complete picture of the impact of adverse events to properly prescribed drugs [5]. According to this study, in 1 year in US nearly 5 million adverse drug reactions were observed, of which more than 2 million were serious, and more than 100,000 were fatal, making this the fourth to sixth leading cause of death in US. The economic aspects are correspondingly high. One study provided an estimate of 76.6 billion dollars for the cost associated with underdosing, overdosing or missed dosing, resulting in increased hospital admissions, lost productivity and premature death, was more than 100 billion dollars.
Furthermore, it is not infrequent that drugs are withdrawn from the market because of side effects that are experienced by extremely small numbers of patients, while the vast majority of patients, might still benefit from the drug. Pharmacogenetics can prevent drug withdrawal by allowing identification of patients at risk of developing a serious adverse reaction. A drug withdrawn from the market a short time after it has been introduced, is a very ineffective use of R&D resource and eliminates a return on substantial investment. Another contribution to side effects reduction could be achieved by applying pharmacogenetics in drug surveillance systems. One way could be to prospectively collect blood samples from a large number of patients when a new drug is introduced to the market. When a rare side effect is experienced by a patient, the corresponding blood sample could be traced back. With time genetic markers might be identified, and pharmacogenetic tests developed, that could predict patients at risk for the adverse event. Another, more simple and immediately applicable way could be to collect a blood samples together with relevant phenotypic information when an adverse event is experienced. If the data and samples are then collected in a unique databank, enough data might be available for studying the genetics of specific adverse events. The potential of pharmacogenetics to predict efficacy is also promising. No drug works on everybody, and so there is a need to better discriminate between the populations that can benefit and those that cannot.

Some scientists wonder why pharmaceutical companies are investing so much in pharmacogenetics, that in principle could reduce market as a result of optimised use of drugs. However, pharmacogenetics will not decrease the number of patients who will benefit from a medicine. Pharmacogenetics will enable patients who are likely to benefit to be identified readily and objectively. Resulting improved cost effectiveness may help governments who are trying to reduce drug expenses to provide a quick, although limited, fix to their deeply in debt national budgets. Pharmacogenetics might provide a new approach, with higher value drugs that are optimally used, that could meet both government and industry needs [6]. Moreover, the application of pharmacogenetics may help pharmaceutical companies to better define the populations to enrol in clinical trials, thus reducing attrition in the R&D pipeline.

3. Pharmacogenomics and its delivery

Pharmacogenomics is expected to deliver new targets for new drugs. Research and development process in recent years has confronted a productivity challenge. The number of new compounds to reached the market has remained steady or even fallen, while R&D expenses have soared. One reason for that is the need to find new, truly disease-related targets for new drugs. According to recent research, all the different molecules that are sold today only account for 503 targets (Fontana A, unpublished data, 2002). With the sequencing of the human genome, the number of possible new targets now numbers in the thousands. For pharmaceutical companies, however, the sequencing achievement, great as it is, is only a beginning. There remains the considerable task of understanding gene function and finding tractable targets.

Other new methods have been introduced in the R&D process, such as combinatorial chemistry and related automated-chemistry techniques, that provide thousands of new compounds and high throughput screening, that can in vitro test these compounds for their chemico-physical and biological properties. However, upstream of these innovative systems, there remains the usual, often time-consuming challenges of optimising lead compounds for their developability as pharmaceuticals and conducting the required animal studies and toxicity testing before clinical trials commence.

Pharmacogenomics can provide new targets from the study of genes involved in diseases. From the knowledge of gene function and of their role in the disease pathway, new targets can be derived, that might be innovative and not accessible with non-genomic approaches. The importance for pharmaceutical companies to find new targets is enormous and possibly related to the likelihood of the company to survive in an increasingly difficult market. As Craig Venter pointed out, companies that do not apply genomics may no more be on the market in 20 years.

4. Pharmacogenetics: a body of literature

Scientific publications in the field of pharmacogenetics are constantly increasing in number. Most of them debate general topics around pharmacogenetics and only a few report new scientific data that may find a clinical application. Nevertheless, important evidences have been reported in many fields.

For example, response to antiasthmatic drugs has been extensively studied. Particularly, polymorphisms in coding regions of the β2 adrenergic receptor gene have been studied and their relevance for a clinical application debated [7–9]. An association has been described between the Arg/Gly polymorphism in position 16 and the response to Albuterol in children [10]. More recently also polymorphisms in non-coding regions of the same gene have been studied. Again in the field of antiasthmatics, associations have been found between polymorphisms in genes encoding for proteins involved in leukotriene synthesis and response to antileukotriene drugs. A polymorphism in the promoter of ALOX5 gene, encoding for 5-lipoxigenase enzyme, that is involved in leukotriene synthesis, has been associated with response to ABT-761, a 5-lipoxigenase inhibitor similar to Zileuton [11]. The same polymorphism has been associated with non-response to zafirlukast, another antileukotriene drug [12]. A polymorphism in leukotriene C4 synthase en-
zyme (LTC4S), again involved in leukotriene synthesis, has been associated with non-response to zafirlukast [12].

These polymorphisms together may explain about 14% of patients not responding to leukotriene antagonists. Because we know that non-responders to leukotriene antagonists exceed this percentage, we have to assume that other genes or non-genetic factors are involved in non-response to this class of drugs.

The observation of an associations between genetic polymorphisms and non-response to different leukotriene antagonists in diagnosed asthmatics, may suggest that these pro-inflammatory mediators do not always play an important role in asthma, and that this may be related to a genetic influence. So, we might speculate that there are at least two types of asthma, one where leukotrienes play a role in disease development, and the other where inflammation is sustained by non-leukotriene mediators.

Another interesting association has been published between CYP2C9 gene, a gene encoding for a drug metabolizing enzyme, and anticoagulation-related outcomes during warfarin treatment [13]. The importance of this finding is related to the direct association established with a parameter actually used in the clinical practice, anticoagulation status, measured by time to therapeutic international normalised ratio (INR).

One of the most interesting reports in the field of pharmacogenetics is related to hypersensitivity to abacavir. Abacavir is used, in association with other drugs, in HIV treatment and is generally well tolerated. However, in some patients (5%) the drug can induce a hypersensitivity reaction that requires permanent discontinuation of abacavir. The reaction requires a clinical diagnosis and doctors and patients have gained enough experience so that this side effect is generally well managed. Some recently published studies have demonstrated that genetic factors play an important role in hypersensitivity development. An association has been found between the human leukocyte antigen (HLA) allele, HLA-B*5701 and hypersensitivity [14]. In a smaller, independent study, an association has also been found between haplotype HLA57.1, a block of HLA genes that are linked and inherited as a group, and hypersensitivity [15]. The 57.1 haplotype was found in 72% of cases (patients that developed hypersensitivity after receiving abacavir) and in none of the controls (patients that received abacavir but did not develop hypersensitivity). However, because the demographics are limited to mostly Caucasian males and the study population is small, these data do not support a clinical application. Their use in a general population may lead to significant morbidity and mortality due to inappropriate confidence being placed in a false negative result. These data clearly demonstrate a role for genetic factors in the development of a hypersensitivity reaction to abacavir.

Extensive research is ongoing in the field, conducted by GlaxoSmithKline and other independent researchers, that may result in the identification of a marker set with sufficient sensitivity and specificity to be clinically useful across diverse patient populations. Even after a marker set is identified, appropriate clinical identification and management of hypersensitivity to ABC must remain the cornerstone of clinical practice.

Many other relevant reports in pharmacogenetics have been published in different areas. However, because it is not in the scope of this paper to provide a comprehensive review of relevant literature in the field, they will not be discussed here.

5. . . and few clinical applications

In spite of fast growing literature, clinical application of pharmacogenetic is still at its very early stage.

Some people speculate that the measure of levels of protein HER2 in breast cancer patient tumor tissue, and the subsequent prescription of Herceptin (generic name Trastuzumab) only to those patients having high HER2 levels, can be regarded as a clinical application of a pharmacogenetic tool. Others believe that this is not a proper example, because not the genotype but the levels of a protein (that in turn is genetically influenced) are measured [16].

Apart from these speculations, the Herceptin example, with an estimate of 97% newly diagnosed breast cancer patients tested, perhaps offers a view of how pharmacogenetic tools can be applied in the clinical setting and of the impact they might have on clinical practice. As for the present, clinical application of pharmacogenetic testing is rare and inconsistent. There are indeed some examples of pharmacogenetic tests available for clinical use: cytochrome P450 and INR test for warfarin, thiopurine methyltransferase test and response to thiopurines, Factor V Leiden test and risk related to the use of oral contraceptives. However, the use of these tests is varied. Why?

There are many reasons. Firstly, the clinical utility of these tests is not always well established. It is frequent that tests are available for use while a lot of questions are still opened with relation to the relevance, utility, applicability, social and ethical impact of the test itself.

Having strong reproduced scientific evidence of a polymorphism influencing response to a drug is essential but not enough for a clinical application.

In the last years many efforts have been produced in the direction of generating valuable scientific data, that in many cases these have indeed been obtained. However, very low attention was paid to exploring relevant issues in translating good genetic science into proper clinical tools. We believe that most of the controversies raised by the availability of some predictive tests, such as BRCA1 and 2 for diagnosis of susceptibility to breast cancer, were originated by the insufficient attention paid to correctly positioning these tests in the clinical environment.

The next phase in pharmacogenetics story will have inevitably to be oriented in this direction, with the aim of
building the connecting link between science and clinical application. This will require an extensive debate involving many skills, as many varied issues need to be considered in a unique approach. Scientific, technologic, clinical, ethical, social, legal, regulatory, proprietary aspects related to availability of a pharmacogenetic test need to be explored and a consensus obtained that can drive clinical application.

This will be the challenge for pharmacogenetics in the future years. Most of the success of pharmacogenetics in its clinical application will be dependent on how successfully this programme will be conducted.

6. Pharmacogenomics: the revolution remaining around the corner

Expectations in the field of pharmacogenomics have been even higher than in the fields of pharmacokinetics. An early paper by Peter Carr edited in 1999 made a forecast of an increase from around 500 to 18,000 for molecular targets in 10 years, as a result of pharmacogenomics application. A previous prediction by an analyst dated 1997 stated that by 2000 companies would have tripled the number of development compounds and halved drug discovery times. This has clearly not occurred.

If we examine the number of development strategies, that is a measure of the number of targets identified for drug development, we observe a constant increase from 1996 [17].

We should conclude that pharmacogenomics have not yet been able to feed the R&D process with new opportunities. However, something indeed has happened.

If we examine the trend of the new R&D projects in the last years, we observe that the number of the new compounds entering the pipeline was 1361 in 1999, decreased to 1253 in 2000 to increase to 1564 in 2001, making this the largest figure since 1980. Although these data must be considered with caution, this might be an indication of pharmacogenomics starting to deliver new compounds. Another positive feature is that development times have been reduced in the period 1996–2000 for all development phases and in a significant manner with respect to the period 1991–1995 [17].

On the other hand, it is clear that the industry continues to suffer from late-stage failures in its clinical programmes.

The first drugs directed at genomics-derived targets are only now emerging. In 1993 SmithKline Beecham, now merged in GlaxoSmithKline, signed a contract agreement with Human Genome Science related to the identification of new compounds through genomic tools. Two compounds have recently been developed that are now undergoing clinical testing. The first compound, named 480848, is an inhibitor of the enzyme lipoprotein-associated phospholipase A2 (Lp-PLA2), an enzyme associated with atherosclerotic plaque, and is now being tested in a phase II clinical programme for the treatment of atherosclerosis. The compound was discovered after the evidence of the role played by Lp-PLA2 in atherosclerosis [18]. The second compound is named 462795, is an inhibitor of cathepsin K, is now undergoing phase I studies, and will be tested for its activity in osteoporosis. The gene encoding cathepsin K is expressed in osteoclasts, and cathepsin K plays a role in osteoporosis.

7. Making a balance

Pharmacogenetics has in the last years produced a body of scientific supporting the role of genetic polymorphisms in drug response. The Pharmacogenetic Working Group gathers 13 among the largest pharmaceutical companies with the aim of debating general issues about pharmacogenetics. Some companies are trying to introduce pharmacogenetic evaluations from the very early stages of drug development, that is from phase I and phase II studies. The aim is to develop pharmacogenetic tests, when this is desirable and feasible, alongside drug development to reduce attrition in the pipeline and then guide clinical practice. This strategy is based on the assumption that pharmacogenetics should be an inherent part of product development. Because we now know that the influence exerted by genetic factors on drug response is the rule, not the exception, this implies that checking this influence should be routine, and trying to develop appropriate pharmacogenetic tests for use in clinical development and, eventually, in clinical practice is the logical consequence.

So, pharmacogenetics is still promising and we should start seeing the first tests used in clinical practice within a few years. It may be, however, that some drugs will never have a pharmacogenetic test associated, because they do not have important efficacy or safety issues to be addressed, or because the influence of genes in drug response is too complex to allow the development of a simply to use test. Pharmacogenetics is an option, not a dictate, and will not immediately pervade clinical practice.

As for pharmacogenomics, the first therapies directly related to this discipline are just now beginning to appear in clinical studies. Yet, pharmacogenomics is now embedded in drug discovery and will remain an essential tool for large pharmaceutical companies. So, what Craig Venter said some years ago, that “pharmaceutical companies not applying genomics will not be on the market in 20 years” seems still reasonable and drives pharmaceutical investments.

8. Note added by the authors after submission

After submission of this paper, on 23 December 2002, the editorial “Pharmacogenetics in the laboratory and the clinic” was issued in the New England Journal of Medicine [19]. In the paper, some of the topics debated in the above article are discussed. The editorial is a highly recommended reading for those who are interested in exploring the potential for clinical application of pharmacogenomics.
References


