Commentary

Safety concerns on the development of novel therapeutic drugs

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Abstract

Along with recent innovative approaches resulting in the development of new therapies such as small molecular inhibitors, therapeutic antibodies, recombinant proteins and gene therapy, there is increasing need for improved understanding of the basic molecular mechanisms that are exploited by such treatments. Helpful tools in the analysis of drug effects include high-throughput screening techniques such as microarrays, which are used in transcriptomics and pharmacogenomics. Although we are far from using these extensive and costly tests in our daily clinical routine, their application in basic research nevertheless takes us closer to individualized therapeutic strategies, in which the optimal therapeutic regimen is identified for each individual patient.

With the current trend toward development of specific, molecular targeted therapies, the translation of basic science research to clinical medicine is more important than ever. However, it is similarly important to take a step back from the bedside to the bench. In the development process, new therapeutic substances are extensively tested *in vitro* and in animal and clinical studies. These tests thoroughly describe the pharmacological and toxicological properties of the drug, but they often fail to grasp the complex effects of a drug on its target cells. In many cases, unexpected negative but also positive effects of a substance are only revealed after longer term clinical use. In this commentary we highlight some possible approaches to analyzing the properties of a substance at the cellular level and to deriving a more complete picture of the impact of a treatment on the human body.

A prime example for bringing basic research results into clinical use lies in the development of anti-tumour necrosis factor (TNF) therapies for patients with rheumatoid arthritis. The anti-TNF approach not only introduced another effective treatment option for rheumatoid arthritis patients but it also gave new insights into the pathological mechanism of the disease. However, the mechanisms of action of anti-TNF agents are still not fully understood, and some of the adverse effects cannot readily be explained. Furthermore, it is not clear why about 30% of patients respond insufficiently to anti-TNF treatment [1]. In light of the costs of biological therapies and their potential side effects, a reliable strategy for identifying nonresponders as soon as possible – ideally even before initiation of therapy – would be of great importance.

In recent years gene expression profiling with microarray technology emerged as a powerful tool with which to elucidate biological pathways in health and disease. It offers the possibility to study simultaneously the expression of thousands of genes and to observe changes in gene expression during pathological states or pharmacological interventions. In order to gain valid information from array experiments, it is crucial first to process accurately the vast amount of raw data generated, but then also to translate purely descriptive array data into information on potentially important and functional biological mechanisms [2]. A number of research groups have analyzed gene expression profiles of patients with rheumatic diseases in order to elucidate pathological mechanism and define potential new drug targets (for review [3]). The same strategy can be used to find differences in gene expression profiles between responders and nonresponders. In juvenile arthritis it could be shown that 2-4 weeks after the onset of treatment the gene expression profile of patients benefiting from the therapy changed toward the profile of healthy control individuals, whereas the profile of patients who turned out to be nonresponders did not [4]. Thus, observation of changes in the transcriptome could help in monitoring the influence of a drug on disease progression and to find the best therapeutic regimen for each individual patient. However, before gene expression arrays can be used to predict response to therapy in clinical practice, their application must become much quicker, cheaper and more user friendly. AlloMap™ (XDx, San Francisco, CA, USA) is an example of a system for monitoring changes in gene expression that may be applied clinically. By measuring the expression levels of 11 different genes associated with immune system pathways in peripheral blood

TNF = tumour necrosis factor.

cells, this assay helps to identify those patients who are at high risk for acute allograft rejection following heart transplantation [5].

Although gene expression studies with whole blood samples or tissues often are biased by variations in cellular composition, *in vivo* analysis of homogenous cell populations under stable conditions facilitates the detection of pathways that are affected by the treatment. In this way, new information about the mechanisms of action and off-target effects of a drug can be gained. An understanding of the molecular mechanisms that are triggered by a substance possibly may widen its field of indication or promote the development of more specific compounds. Another advantage of testing sorted cell populations is the ability to determine the contribution of a single cell type to the overall effect. Thereby, new information about pathophysiological mechanisms can be gained and differences in the activation of human and animal cells detected. This is of special interest for novel therapeutic strategies that are specifically designed for the human environment, such as small molecular inhibitors, but also for agonistic antibodies, recombinant proteins and gene therapy approaches. In this setting, results from animal studies can be misleading because the treatment response in animals can differ considerably from that in humans. A recent example of such a mismatch is the application of a CD28 agonistic antibody. Although tests in animals showed a selective activation of regulatory T cells, application in humans led to a life-threatening immune reaction [6]. Whether this potent adverse effect was due to a cytokine storm triggered by activated helper T cells, as suggested by the developer, or was due to some other mechanisms is not yet clear.

In order to mimic the response of the human immune system to a therapeutic antibody, 'humanized' animal models such as immunodeficient mice reconstituted with a human immune system could be applied in the future. Recently developed humanized mouse models have considerable levels of engraftment and the achieved reconstitution is almost absolute. However, the degree to which the different parts of the immune system are functional has not yet been determined [7]. Therefore, it remains to be clarified whether such models can actually be used to improve the safety of testing immunomodulatory pharmaceuticals in humans.

A novel approach to finding the optimal treatment for each individual patient is pharmacogenomics, in which genetic polymorphisms in drug-metabolizing enzymes, drug transporters, or drug targets are studied and linked to the patient's response to a drug. A number of studies have been conducted in rheumatoid arthritis patients with the aim of predicting response to therapy on the basis of genetic variations. Polymorphisms in methotrexate transporter genes and in several other key genes in the methotrexate pathway have been reported to be associated with the efficacy and toxicity of the drug [8]. Similarly, it was shown that polymorphisms in the TNF promoter and/or the TNF receptor II probably influence response to anti-TNF treatment, as did genetic variations in the interleukin-10 promoter and the Fcγ receptor IIIA [9-12]. However, the results of the various pharmacogenomic studies in rheumatoid arthritis are not sufficiently conclusive to justify the introduction of this technology into clinical practice. The field could take a big step forward with the use of high-throughput technology; with a DNA microarray it is possible to screen for thousands of single nucleotide polymorphisms in one experiment. In addition, recent efforts such as the HapMap project – a database of genetic variations associated with human diseases and response to pharmaceuticals – may shed light on poor response to disease-modifying drugs in some patients with rheumatoid arthritis.

The development of innovative therapeutic strategies such as small molecular inhibitors, therapeutic antibodies, recombinant proteins and gene therapy poses a challenge for traditional testing methods, in particular for animal studies [13]. High-throughput techniques such as microarrays could be applied to learn more about the effect of a therapeutic substance at the cellular level and about pathological mechanisms of the treated disease. Although most of these new methods are not yet ready for routine clinical use, the comprehensive knowledge gained in currently ongoing research will in the future provide the expertise necessary to select the best drug for each individual patient.

Competing interests

The authors declare that they have no competing interests.

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