Personalized Medicine in Rheumatoid Arthritis
Hopes and Challenges

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Abstract
Clinicians have an increasing number of therapeutic agents available for the treatment of rheumatoid arthritis (RA). Pharmacogenetics, the study of genetic variation underlying differential response to drugs, seeks to improve treatment of individual patients. Multiple markers of treatment response have been analyzed in RA, but many of the studies are small and retrospective in nature. There are many obstacles to personalized medicine for RA patients, including incomplete understanding of disease pathogenesis, affecting changes in physician behavior, and acceptance of costs by health insurers. Despite these many obstacles, there are many reasons for optimism for future personalized medicine in RA. There have been remarkable advances in genomics, proteomics, and statistical analyses of large amounts of data. The goal of identifying genetic, serum, and clinical factors that allow profiling of individual patients to predict optimal treatment regimens is a worthy pursuit which will hopefully improve clinical care of RA patients.

Clinicians have an increasing number of therapeutic agents available for the treatment of rheumatoid arthritis (RA) (Table 1). In addition to traditional disease-modifying anti-rheumatic drugs (DMARDs), there are now three FDA-approved anti-TNF agents (infliximab, etanercept, and adalimumab), as well as treatments directed against interleukin (IL)-1 (anakinra), T cells (abatacept), and B cells (rituximab). Additional new drugs, including those directed at IL-6, IL-15, and other targets, are on the horizon. Nobel laureate Paul Ehrlich applied the term “magic bullets” to describe antitoxins and antibacterial substances that are uniquely effective, because they destroy only those targets against which they are directed. Although there is no magic bullet, advances in genomics, pharmacology, disease pathogenesis, biotechnology, and biostatistics have made the goal of tailored therapy for individual patients seem less whimsical.

In 1959, Vogel coined the term pharmacogenetics to describe inherited differences in drug responses. Inherited deficiency of glucose-6-phosphate dehydrogenase (G6PD) was shown to cause severe hemolysis seen in some patients exposed to the antimalarial drug primaquine. This discovery explained why hemolysis was observed mainly in African-Americans, in whom the deficiency is common, and rarely in Caucasians of Northern, Western, and Eastern European descent. Pharmacogenetics, the study of genetic variation underlying differential response to drugs, seeks to improve treatment of individual patients by addressing several questions. For an individual patient, will the drug relieve symptoms and alter the course of the disease in this patient? What is the optimal dose of the drug for this patient? Will the drug cause side effects in this patient? What is the optimal dose of the drug for this patient? Will the drug cause side effects in this patient?

Most patient populations show large inter-individual variability in drug response and toxicity. Individuals may have excellent responses, respond partially, or experience adverse drug reactions to standard doses. Drug concentrations in plasma can vary more than 600-fold between two individuals of the same weight on the same dosage. This variation can be due to genetic, physiological, pathophysiological, or environmental factors. A drug’s absorption, distribution and metabolism, and interactions with its target can be determined by genetic differences. Genetic factors account for 15% to 30% of differences in drug
metabolism and response between individuals. For some drugs or classes of drugs, genetic factors can account for up to 95% of inter-individual variability in drug disposition and effects. Potential pharmacogenetic markers may be in genes involved with the drug target, the metabolism of the drug, or in the disease pathway. With regard to the influence of markers on drug metabolism, the effect may lie in a Phase 1 reaction (e.g., cytochrome P450 enzymes), in a Phase 2 reaction (e.g., N-acetyl transferases), or in the biologic pathways for biologic agents (e.g., Fc receptor for monoclonal antibodies).

Clinicians treating RA face several problems, including the lack of clinical characteristics or laboratory tests that reliably predict severity of disease or phenotype (e.g., extra-articular manifestations). Potential predictors of outcomes in RA include clinical factors, such as poor functional status as assessed by the Health Assessment Questionnaire, or a higher number of swollen or tender joints; environmental factors, such as cigarette smoking; socioeconomic factors, such as lower income or educational level; serologic factors, such as rheumatoid factor, anti-CCP antibody, or elevated baseline ESR (erythrocyte sedimentation rate) or CRP (C-reactive protein); radiographic factors, such as the presence of joint erosions at baseline; or genetic factors, such as the presence of the HLA-DRB1 shared epitope in Caucasians. Another problem is that improvement in symptoms may not alter the course of the disease (such as bony erosions, joint deformity). In addition, none of the currently available medications is universally effective and free of side effects. Although clinical trials yield data on frequency of treatment response in a group of subjects, there are as yet no predictors of treatment response that are clinically useful in individual patients. Because of the variety of new drugs, their cost, and incomplete information on side effects, such as susceptibility to infections, the need for markers of treatment response (as defined clinically, radiographically, and functionally) is increasing.

What lessons have been learned in research on non-rheumatic diseases? A diagnostic multi-gene expression test, Oncotype DX™ (Genomic Health, Inc., Redwood City, California), has shown promise in predicting the likelihood of cancer recurrence, the likelihood of patient survival within 10 years of diagnosis, and the likelihood of chemotherapy benefit in breast cancer patients with no involved lymph nodes and estrogen-receptor-positive tumors. Using a reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay on breast cancer tissue, a recurrence score ranging from 0 to 100 is derived based on the expression of 16 genes relative to 5 reference genes. Based on recurrence scores, each patient is assigned to a risk group (low, intermediate, or high). In a multivariate Cox model, the recurrence score provided significant predictive power that was independent of age and tumor size (p < 0.001).

Another example in which genetics may be valuable is the use of the epidermal growth factor receptor (EGFR) kinase inhibitor, gefitinib, in advanced lung cancer. Initially, the effectiveness of gefitinib in advanced lung cancer was disappointing. However, further analysis revealed that in approximately 10% of patients, lung tumors responded well. The difference in patients who respond well is the presence of specific mutations in the receptor for epidermal growth factor.

Unlike the two examples cited above, the case of thiopurine S-methyltransferase (TPMT) is more directly relevant to the rheumatic diseases. TPMT catalyzes S-methylation of thiopurine drugs 6-mercaptopurine (6-MP) and azathioprine (AZA). TPMT activity in red blood cells is controlled by a common polymorphism. Approximately one in every 300 subjects lacks TPMT activity, and about 11% of subjects have intermediate activities. Among children with acute lymphoblastic leukemia (ALL), assessment of TPMT genetics is a clinically useful test in calculating dosages of 6-MP that will be efficacious and nontoxic. TPMT and azathioprine toxicity was studied in rheumatic diseases by Black and colleagues. A prospective cohort study was performed in two rheumatology units. Azathioprine was prescribed for 67 patients: 49 with rheumatoid arthritis, seven with SLE, and 11 with other rheumatic diseases. Six of 67 patients (9%) were heterozygous for TPMT *3A. Among these six patients, five discontinued azathioprine

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<th>Table 1 Drugs Used in the Treatment of Rheumatoid Arthritis</th>
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<td><strong>Nonsteroidal Antiinflammatory Drugs</strong></td>
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therapy within one month because of low leukocyte counts. The sixth patient was noncompliant. Patients with wild-type TPMT alleles received therapy longer than patients with mutant alleles (median duration of therapy, 39 weeks versus 2 weeks, respectively), demonstrating the usefulness of assessment of TPMT alleles prior to azathioprine therapy.

In RA, multiple markers of treatment response have been analyzed. HLA-DRB1 alleles encoding the RA shared epitope, for example, have been assessed as pharmacogenetic markers. Analyses of the roles of polymorphisms in TNF, TNF receptors, Fc receptors, and other genes in treatment response to TNF inhibitors have given conflicting results, likely for many reasons. Many studies have small numbers; are retrospective in nature; may not fully account for the impact of differences in baseline DMARD therapy or changes in DMARDs or corticosteroids during the treatment period; consider use of multiple different TNF inhibitors; may include subjects of different ethnicities, in which minor allele frequencies may vary; may use different definitions for drug responsiveness; and have different treatment periods, among other variations. Markers of treatment response and toxicity of methotrexate (MTX) in RA have also been of considerable interest.

There are many obstacles to personalized medicine for RA patients. These hurdles fall into several categories, such as those relating to disease pathogenesis, to physician behavior, and to the goals of pharmaceutical companies and health insurers. Among the barriers to individualized therapy for RA patients is the lack of a clear understanding of the pathogenesis of the disease. Unlike other diseases, such as breast cancer, affected tissue is seldom obtained early in the course of the disease, so pathogenic subtypes of synovitis are difficult to define. The drug-response phenotype is very complex, especially with the use of small-molecule drugs such as MTX, in which multiple pathways may be involved. There are few, if any, large databases of RA patients with similar phenotype (e.g., autoantibody status, HLA-DRB1 status, disease duration, or previous DMARD therapy) which have collected information regarding possible confounders (drug interactions, diet, smoking, etc.); in which patients are given standardized treatment regimens; and in which standardized outcome measures have been applied. This limits the statistical power of the analyses of markers of treatment responses.

Another area in which much work needs to be done to realize personalized medicine in RA is that of physician behavior. As a rule, clinicians are educated to start treatment with the default average dose, except in special cases such as advanced age or renal failure. Pharmacogenomics entails ordering and interpreting laboratory tests, which can be time-consuming and require education. Furthermore, the diversity of genetic polymorphisms (SNPs/single nucleotide polymorphisms, insertions/deletions, splice variants, etc.) makes providing definitive results for even a single gene challenging. The ideal test would predict the best therapeutic alternative by quickly, accurately, and cheaply providing a composite profile. Until researchers achieve tests that provide a fast and accurate answer and are simple to administer and interpret, testing to stratify patients based on the likelihood of treatment response will not be commonly used in the clinic.

Another problem is that, to date, molecular technology has not been incorporated into well-controlled and monitored clinical trials. There is often difficulty in controlling for nongenetic confounders (drug interactions, diet, smoking) in these trials, and there is little funding as well for large-scale pharmacogenomic studies. In general, pharmaceutical companies’ legal and marketing departments fear that obtaining knowledge of markers of treatment response will possibly lead to profitable tests for outside entities and possibly limit their drug’s use and profitability. Thus, health care agencies must accept the added costs that will be incurred during the transition to genetically guided decisions about drug therapy. Although the Oncotype DX test cited above costs about $3400 per patient, in the long-run, it saves society money by decreasing the likelihood of adverse drug effects and increasing the probability of successful therapy. Pharmacogenomics has the potential to facilitate this process by translating knowledge of human genome variability into better therapeutics.

Despite these many obstacles, there are many reasons for optimism for future personalized medicine in RA. With the completion of the Human Genome Project and the rapidly expanding HapMap (haplotype map of the human genome) data, in conjunction with improved methods of proteomics, genomics, and statistical analysis, genotyping and the analyses of results are capable of being performed more efficiently and at lower cost. In addition, pharmaceutical companies are providing additional targeted therapies to allow more focused experimentation into mechanisms of action. Finally, if cost-effectiveness analyses show an advantage to testing prior to treatment, third-party payers will take notice and physician behavior will change.

In summary, despite tremendous advances, we have not yet found a magic bullet for RA. Such a drug would be 100% effective in all RA patients, have no side effects, be easily administered, nonperishable, and be long-acting or even curative. The goal of developing such a drug or drugs may be a pipe dream, but identifying genetic, serum, and clinical factors that allow profiling of individual patients to predict optimal treatment regimens is a worthy pursuit. Although no perfect tests will be available, research in the field of pharmacogenetics will surely improve clinical care of RA patients by allowing more rational strategies for the approach to drug therapy.

Disclosure Statement
The author does not have a financial or proprietary interest in the subject matter or materials discussed in the manuscript.
including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

References