Understanding personalized medicine in rheumatoid arthritis: a clinician's guide to the future

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Abstract: Personalized medicine refers to the utilization of technologies at the molecular level to understand disease processes and improve health outcomes. In rheumatoid arthritis (RA) some factors associated with disease outcome have been identified. These factors have not yet been integrated into a clinically useful tool to predict disease outcome in individual patients. Developments in pharmacogenomics are moving the field forward quite rapidly. Genetic variants, which may have a role in drug metabolism mediating either drug response or toxicity, have been identified for both traditional disease modifying antirheumatic drugs and biologic agents. Choosing a medication based on a patient's characteristics (sociodemographic, clinical, genetic) will result in better utilization of resources and better clinical outcomes. The ethical, political, and legal implications of personalized medicine need to be considered as well.

Keywords: biomarkers, disease-modifying antirheumatic drugs (DMARDs), personalized medicine, pharmacogenetics, pharmacogenomics

Introduction

Rheumatoid arthritis (RA) is the most common inflammatory arthritis, affecting ~1% of the US population. Multiple disease modifying antirheumatic drugs (DMARDs) and eight biologic agents are currently approved by the United States Food and Drug Administration (FDA) for treatment of RA. No drug is effective in every patient, and there is great variability in toxicity and price, which varies from ~\$400/year for methotrexate (MTX) to up to \$15,000/year for biologic agents. Thus, the next major advance in the treatment of RA is not additional drugs, but rather a dramatic improvement in the efficacy and cost-effectiveness of drugs for individual patients. One of the hopes for modern medicine is the realization of 'personalized' medicine, which allows accurate, quick prediction of the most efficacious, least toxic, and least expensive drug for an individual patient. Identifying predictors of treatment response in RA will lead to rapid, early institution of optimal drugs rather than a 'hit or miss' sequential approach, reduce adverse events, improve patient compliance, and lead to substantial reduction in the cost of healthcare.

The term personalized medicine has become common parlance over the last few years. This concept generally refers to the utilization of technologies to understand disease processes at the molecular level in order to improve healthcare as it is applied to individual patients [Jain, 2002]. Ideally, decisions about choice of treatment for a particular disease should be based on the individual patient's characteristics, including age, gender, body mass index, diet, environment, and genetic profile. Advances in pharmacogenomics, made possible by the sequencing of the human genome and by our ability to assess natural genetic variation, have brought this issue to the forefront. New questions have emerged regarding the search for better diagnoses, more effective treatments, and the reduction of healthcare costs.

The concept of pharmacogenetics is not new, as Vogel coined the term in 1959 to describe inherited differences in drug responses [Vogel, 1959]. Genetic variation can affect not only how patients respond to treatment; it also affects drug metabolism and its processing in the body. Thus, personalized medicine also includes the study of metabolomics, or the screening for metabolites

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and the assessment of metabolic pathways helping in the identification of the right phenotype; it also includes screening for protein changes/biomarkers (proteomics) and monitoring for disease progression as result of different treatments. Thus, multidisciplinary strategies provide an interactive process in which findings are translated into novel therapies; this information can be specifically used to stratify diseases, select between different medications, and tailor dosages.

At the present time, there are several examples of using genetics to predict whether a patient will have a better response to certain drugs. For example, genetic testing of thiopurine S-methyltransferase (TPMT), the enzyme that catalyzes S methylation of thiopurine drugs such as 6-mercaptopurine (6-MP) and azathioprine (AZA), is relevant for its prescription. The activity of TPMT in red blood cells is controlled by common polymorphisms that have been studied in relation to AZA toxicity. Patients with the wild type TPMT alleles tolerated therapy longer than patients with the mutant alleles, who frequently developed low leukocyte counts [Black *et al.* 1998]. In this and other cases, patients could be tested prior to prescribing the drug; those patients who are unlikely to benefit from them are saved the expense and possible toxicity. Patients who will likely benefit from them, on the other hand, receive them with a high level of confidence that they will have a good outcome. This approach could even allow drugs that might be taken off the market because of their side effects to be given safely to those who are unlikely to experience an adverse reaction.

Indeed, the contribution of genetic variation to effective drug therapy is also affecting how drugs are developed and marketed. If drug developers understand the contribution of genetic variation to the effectiveness of a drug, they could test drugs in much smaller groups of subjects likely to respond to the treatment with minimal side effects. This could make drugs that would otherwise not be seen as valuable to be available to those who need them, and potentially reduce the cost of drug trials.

In regards to RA, the efficacy of treatment with DMARDs, especially traditional DMARDs, such as MTX, sulfasalazine (SSZ) and leflunomide are well known [Smolen *et al.* 1999; Strand *et al.* 1999]. Over the past few years, new drugs used alone or in combination have been

developed, increasing the possibility of better outcomes for patients with RA; these are the so-called biologic treatments and are directed to different cytokines, interleukins, and cell receptors crucial in autoimmunity. The biologics approved by the FDA are the anti-tumor necrosis factor (TNF) compounds: etanercept, infliximab, adalimumab, certolizumab and golimumab; an IL-1 receptor antagonist: anakinra; a CTLA4-Ig fusion protein: abatacept; and the antiCD20 antibody: rituximab. In addition a number of anti-TNF compounds are under development, as well as an antibody directed against the IL-6 receptor: tocilizumab. The use of these agents alone and in combination with traditional DMARDs has been limited by unpredictable toxicities and different responses rates [Padyukov *et al.* 2003]. How recent advances in pharmacogenomics (knowledge about toxicity, severity profile and cost) could affect our therapeutic decisions is discussed below.

Clinical predictors useful for personalized medicine in RA

There is significant variability in the course and progression of joint damage in RA; the identification of patients who will progress rapidly is required to avoid permanent damage and prevent disability and diminished survival. The variability in the course of the disease and the dissociation between the clinical symptoms and progression of bone destruction has made it hard to identify predictors of disease activity or response [Emery *et al.* 2008; Roux-Lombard *et al.* 2001; Voskuyl and Dijkmans, 2006].

Potential predictors include clinical, environmental, laboratory parameters, and genetic markers. Previously identified clinical predictors are the Health Assessment Questionnaire (HAQ), the number of swollen and tender joints, and the lack of response to traditional DMARDs within 6 months [Bridges Jr, 2007; Smolen *et al.* 2006]. Environmental and laboratory parameters identified as predictors of disease progression include smoking, lower educational level, low socioeconomic status; rheumatoid factor (RF) and anti-cyclic citrullinated peptide (antiCCP) antibodies positivity, higher erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) levels, and the presence of erosions at baseline. In addition, the *HLA-DRB1* shared epitope has been recognized as being associated with disease severity and susceptibility [Bridges Jr, 2007; Smolen *et al.* 2006].

The knowledge of the severity profile in RA patients, based on specific predictors, is the first step to make a therapeutic decision; in addition, it is necessary to determine the predictors of efficacy and toxicity to both traditional DMARDs and biologic agents. All medications have the potential to produce side effects; the ability to identify those patients who will benefit the most with biologics is imperative, given the high cost of these medications, their increased use, and the development of new compounds aimed at specific target molecules in the pathway of RA.

Pharmacogenetics in RA

Traditional DMARDs

MTX is the most common DMARD used in RA, since it is relatively safe, efficacious, and inexpensive. This drug can be used alone or with a wide variety of other DMARDs; however, approximately 30% of RA patients fail MTX since we cannot predict as yet who will have a good therapeutic response. This is in part due to the fact that the mechanism of action of MTX is not totally understood and markers for treatment response have not been consistently validated. Furthermore, there is significant difficulty in assessing confounding factors such as disease duration, previous medication failure, compliance with dosing regimens, etc [Bridges Jr, 2004].

The mechanism of action of MTX in RA probably relates to its ability to increase ultimate release of endogenous adenosine. Different polymorphisms in diverse steps in MTX metabolism have been studied and include polymorphism in genes that control the transport of MTX [Drozdik *et al.* 2006; Pawlik *et al.* 2004; Ranganathan *et al.* 2008; Takatori *et al.* 2006]; cellular enzymes in the folate [Dervieux *et al.* 2006; Hider *et al.* 2007; Hughes *et al.* 2006; Kumagai *et al.* 2003; Kurzawski *et al.* 2007; van Ede *et al.* 2001]; and adenosine pathways [Wessels *et al.* 2006]. The most important pharmacogenetic studies for traditional DMARDs are depicted in Table 1.

One of the enzymes that has been intensely studied is methylene tetrahydrofolate reductase (*MTHFR*); when this enzyme is deficient, it is associated with hyperhomocysteinemia with consequent damage to the peripheral vascular and central nervous systems [Schwahn and Rozen, 2001]. About 10 polymorphisms in the

MTHFR gene have been studied suggesting that 677C/T and 1298A/C single nucleotide polymorphisms (SNP) are associated with a reduction on the activity of this enzyme and, therefore, could be markers for MTX toxicity or efficacy [Berkun *et al.* 2004; Frosst *et al.* 1995; Ranganathan *et al.* 2008; Ulrich *et al.* 2002; Urano *et al.* 2002; van Ede *et al.* 2001]. Additional genes associated with toxicity to MTX are being investigated at the present time. In short, this genetic information could produce a better predictive model of efficacy and toxicity.

Another conventional DMARD is SSZ, which is often used in RA with a rate of toxicity of 20–30%. This drug is constituted by 5-aminosalicylic acid (5-ASA) and sulfapyridine and is reduced by colonic bacteria. Sulfapyridine is absorbed and metabolized in the liver by acetylation [Pullar *et al.* 1985]. *N*-acetyltransferase (NAT) has two isoenzymes: NAT1 and NAT2. NAT2 is responsible for acetylation of SSZ. The rate of acetylation is genetically represented by a bimodal distribution with patients classified as slow or rapid acetylators. The presence of different haplotypes, specifically NAT2*4, results in a rapid acetylator phenotype while other haplotypes result in a slow acetylator phenotype [Blum *et al.* 1991; Hickman and Sim, 1991]. The slow acetylator phenotype has been associated with a higher rate of side effects [Tanaka *et al.* 2002], suggesting that testing for *NAT2* could be used to reduce the incidence of drug toxicity.

Leflunomide is an isoxazol with an efficacy comparable to MTX [Strand *et al.* 1999]; its mechanism of action is by inhibiting the dihydroorotate dehydrogenase (DHODH). The C allele of rs3213422, located in *DHODH*, has been associated with response to leflunomide [Pawlik *et al.* 2009].

Biologic agents in RA

TNF inhibitors have been reported to inhibit radiographic bone lesions of RA more effectively than traditional DMARDs [Lipsky *et al.* 2000]. Not all patients experience optimal responses to these drugs, with about one third of them maintaining high disease activity (non responders). Among those who respond, most exhibit a partial response rather than complete remission [Padyukov *et al.* 2003]. Different factors can explain the variable response to these compounds including genetic, physiological and

Table 1. Pharmacogenomic studies in patients with rheumatoid arthritis treated with traditional disease-modifying antirheumatic drugs.

Drugs	[SNP] gene	Response/toxicity	Reference
Methotrexate	[3435C>T] MDR1	TT genotype is associated with high remission rate	[Drozdzik <i>et al.</i> 2006; Pawlik <i>et al.</i> 2004]
	[3435C>T] MDR1 [1236C>T] ABCB1, [23 + 56T>C] ABCC2, [1249G>A and 1058G>A] ABCC2 and [2677C>T] MTHFR	TT genotype is associated with nonresponder status Genotypes are associated with overall toxicity (especially hepatic, intestinal and alopecia) with variable frequency in different ethnic groups	[Takatori <i>et al.</i> 2006] [Ranganathan <i>et al.</i> 2008]
	[-401CC] GGH, [347GG] ATIC, [1298AC/CC] MTHFR, [2756AA] MS, [66GG] MTRR	Genotypes are associated with toxicity	[Dervieux <i>et al.</i> 2006]
	[34TT] AMPD1, [347CC] ATIC, [94CC] ITPA [677T-1298A] MTHFR	Genotypes are associated with a good clinical response	[Wessels <i>et al.</i> 2006]
	[1298CC] MTHFR [677C/T] MTHFR [677T, 1298C] MTHFR	Genotypes are associated with toxicity CC genotype is associated with toxicity TT or C/T are associated with toxicity	[Ulrich <i>et al.</i> 2002] [Berkun <i>et al.</i> 2004] [van Ede <i>et al.</i> 2001]
Sulfasalazine	[1289A, rs4846051C] MTHFR [677T-1298A] MTHFR [TSER*2/*3] TYMS, [347CG] ATIC, (806A) SLC19A1 NAT2	Genotypes are associated with a good clinical response Genotypes are associated with toxicity Genotypes are not associated with toxicity or efficacy Genotypes are associated with diminished activity Slow acetylator phenotype is associated with toxicity	[Kurawski <i>et al.</i> 2007] [Hughes <i>et al.</i> 2006] [Kumagai <i>et al.</i> 2003] [Dervieux <i>et al.</i> 2005] [Pullar <i>et al.</i> 1985; Tanaka <i>et al.</i> 2002]
	[19C>A] DHODH	C allele is associated with a good clinical response	[Pawlik <i>et al.</i> 2009]
Leflunomide			

ABCB1, multidrug resistance 1; ABCC2, multidrug resistance 2; AMPD1, adenosine monophosphate deaminase; ATIC, aminimidazole carboxamide ribonucleotide transformylase; DHODH, dihydroorotate dehydrogenase; GGH, gamma-glutamyl hydrolase; ITPA, inosine triphosphate pyrophosphatase; MDR1, multidrug resistance 1; MS, methionine synthase; MTHFR, methylentetrahydrofolate reductase; MTRR, methionine synthase reductase; NAT2, N-acetyltransferase 2; SLC19A1, solute carrier family 19 (folate transporter); TYMS, thymidylate synthetase.

environmental factors. Despite the fact anti-TNF therapy is an outstanding tool to treat RA, it has a higher cost than traditional DMARDs. In addition, these compounds can affect the host resistance to infection as well as impede immunosurveillance [Cohen *et al.* 2006]. Several studies have identified candidate genes [Coenen *et al.* 2007] and biomarkers of response to anti-TNF such as *HLA-DRB1* alleles, *TNF*-alpha polymorphisms, lymphotoxin alpha (*LTA*), interleukin-10 (*IL10*), transforming growth factor beta1 (*TGFB1*), IL1 receptor antagonist (*IL1RN*), *TNF* receptors, and *Fcγ* receptors. As shown in Table 2, results have been inconsistent, probably due to the heterogeneity of the studies including different baseline and concomitant treatments (DMARDs), different inclusion criteria, and small number of patients. For example, a good clinical response and the combination of the alleles -308 *TNF* G/G and 1887 *IL10* G/G was reported by Padyukov *et al.* in 123 patients [Padyukov *et al.* 2003], whereas in a 1-year follow up study of 457 patients with early RA treated with etanercept (25 mg twice a week or 10 mg twice a week) without concomitant DMARDs, the presence of two shared epitope alleles and variants in the *LTA-TNF* gene were associated with better response to etanercept [Criswell *et al.* 2004]. The association of *TNF* -308 G/G alleles and response to infliximab and etanercept have been document in several studies [Cuchacovich *et al.* 2006; Fonseca *et al.* 2005; Kang *et al.* 2005; Miceli-Richard *et al.* 2008; Seitz *et al.* 2007]; however, in studies of patients with longstanding RA treated with infliximab plus DMARDs, this association could not be corroborated [Marotte *et al.* 2006; Martinez *et al.* 2004; Pinto *et al.* 2008].

Other polymorphisms have been explored as potential markers of response or toxicity to these agents. For example, the genes encoding Fc gamma receptor IIIA (*FCGR3A*) and *TNF* receptor p75 (*TNFRSF1B*) have been studied with inconclusive results [Canete *et al.* 2008; Kastbom *et al.* 2007; Rooryck *et al.* 2008; Toonen *et al.* 2008; Tutuncu *et al.* 2005]. In addition, in a genome-wide association study, a search for different SNPs associated with response to anti-TNF in RA was recently reported. The investigators reported that SNPs in v-maf musculoaponeurotic fibrosarcoma oncogene homolog B (*MAFB*), type I interferon (*IFNk*), and paraoxonase I (*PON1*) were

significantly associated with anti-TNF response [Liu *et al.* 2008].

Gene expression studies in peripheral mononuclear cells have been performed for treatment response markers in RA. In one study, eight gene transcripts were found to be predictors of response after 3 months of anti-TNF therapy [Lequerre *et al.* 2006]. In another study, a different expression of interferon (IFN)-related genes resulted in their inhibition and was associated with good response. Additionally, the expression in other genes at baseline was different in responders than in nonresponders [Sekiguchi *et al.* 2008]. The assessment of expression of individual cytokine, chemokine, and metalloproteinase proteins during anti-TNF therapy has not resulted in the identification of markers of good outcome [Buch *et al.* 2008; Catrina *et al.* 2002]. Baseline differences for MCP-1 and EGF were found in one study [Fabre *et al.* 2008], and a member of TNF family (TNF-related weak [TWEAK]) has shown possible therapeutic potential in a murine model. Several studies have been performed in search of predictors of clinical response to anti-TNF agents at the synovial tissue level; however, the need to perform biopsies to obtain synovial tissue samples makes this approach difficult to implement and thus of limited clinical applicability [Koczan *et al.* 2008; Lindberg *et al.* 2006].

Response to rituximab, an anti-CD20 monoclonal antibody, has been weakly associated with circulating levels of CD20+ B cells [Dass *et al.* 2008; Kavanaugh *et al.* 2008]. Other subpopulations of B cells have been associated with relapses [Leandro *et al.* 2006; Roll *et al.* 2008], but more genetic studies have been published in relation to the drug's effect in B cell malignancies, for which it was originally approved.

Abatacept (CTLA4-Ig) has been associated with a reduced expression of cytokines such as IFN- γ , IL- β , and others in the synovial membrane [Buch *et al.* 2009].

A clinician's guide for the future

Results of translational research directed at personalized medicine in RA have been somewhat disappointing to date for several reasons. First, disease phenotypes in RA are not always clear; multiple phenotypes can result from the same genotype or vice versa. Second, RA is a complex disease with multiple genes involved in response

Table 2. Pharmacogenomic studies in patients with rheumatoid arthritis treated with anti-tumor necrosis factor agents.

Drugs	(SNP) gene	Response/toxicity	Reference
Etanercept	HLA-DRB1, LTA-TNF (-308G/G) TNF- α	Genotypes are associated with response to treatment in early RA Genotype is associated with better responses than -308A/G	[Criswell <i>et al.</i> 2004] [Fonseca <i>et al.</i> 2005; Maxwell <i>et al.</i> 2008]
Infliximab	(158V/F) FCGR3A (-308) TNF- α , (-1087) IL10 (-857C/T) TNF- α IL1B, IL1-RN, TNF- α HLA-DRB1, HLA-DQA1, HLA-DQB1 and BAT2 HLA-DRB1, TNF- α (158V/F) FCGR3A (196M/R) TNFRSF1B (-238G/A) TNF- α (131R/H) FCGR2A, (158F/V) FCGR3A	No association with clinical response Genotypes are associated with a good clinical response Genotype is associated with good clinical response Genotypes are not associated with clinical response Genotypes are associated with good clinical response No association with treatment response No association with treatment response Genotype is associated with treatment response Genotype is associated with poorer response Both genotypes influence treatment response	[Kastbom <i>et al.</i> 2007] [Padyukov <i>et al.</i> 2003] [Kang <i>et al.</i> 2005] [Marotte <i>et al.</i> 2006] [Martinez <i>et al.</i> 2004] [Pinto <i>et al.</i> 2008] [Kastbom <i>et al.</i> 2007] [Rooryck <i>et al.</i> 2008] [Maxwell <i>et al.</i> 2008] [Tutuncu <i>et al.</i> 2005]
Adalimumab	(-308G/G) TNF- α (-238G/-308G/-857C) TNF	Genotype is associated with a good clinical response	[Cuchacovich <i>et al.</i> 2006]
Any anti-TNF*	(-308G/G) TNF- α (676T>G) TNFSF1B MAFB, IFN- γ , PON1, IL10	GG genotype is associated with diminished treatment response GG genotype is associated with better response than A/G or A/A Genotype is not associated with treatment response Genotypes are associated with good clinical response	[Miceli-Richard <i>et al.</i> 2008] [Seitz <i>et al.</i> 2007] [Toonen <i>et al.</i> 2008] [Liu <i>et al.</i> 2008]

BAT2, HLA-B associated transcript 2; FCGR, Fc-gamma receptor; HLA-DQA1, major histocompatibility complex, class II, DQA1; HLA-DQB1, major histocompatibility complex, class II, DQB1; HLA-DRB1, major histocompatibility complex, class II, DRB1; IFN, interferon; IL10, interleukin 10; IL1B, interleukin 1 β ; IL1RN, interleukin 1 receptor antagonist; LTA, lymphotoxin- α ; MAFB, V-me1 musculoaponeurotic fibrosarcoma oncogene homolog B; MICA, MHC class I chain-related gene A; PON1, paraoxonase I; TNF, tumor necrosis factor.

*Studies with more than one anti-TNF.

(efficacy and toxicity) to drugs. Third, as opposed to cancer, in which the affected tissue is generally available for analysis, RA synovial tissue is not obtained as part of routine diagnosis. Thus, studies in RA have focused on peripheral blood as a surrogate tissue, which may not reflect pathogenetic events in the synovial tissue.

Major explanations for the heterogeneity of the published studies probably relate to their relatively small sample size, differences in baseline and concomitant therapies including DMARDs and glucocorticoids, and inclusion of patients from different racial/ethnic groups. The role of ethnicity is potentially important since allele frequencies vary as a function of racial/ethnic group; therefore, it is necessary to conduct large studies of well characterized RA patients from differentiated racial/ethnic groups before definitive conclusion can be reached.

Therefore, it is not yet possible to provide definitive recommendations to clinicians with regard to genetic testing, serologic tests, or algorithms to guide treatment of patients with RA.

However, personalized medicine, as described, will be possible as the cost of genotyping continues to fall; thus more patients will receive proper treatment and fewer patients may be necessary in clinical trials. In the future, highly accurate, inexpensive, and rapid tests, which can be performed at the time of diagnosis, will be available to determine the patient's best treatment choice in terms of safety and toxicity profiles. Such testing is already being performed in other disciplines such as oncology and psychiatry. For example, in patients with treatment-resistant depression (lack of response or severe side effects), polymorphisms of cytochrome P450 (a hepatic enzyme crucial for the metabolism of many drugs) such as the *2D6* and *2C19* alleles, as well as for other genes, are being examined to allow better selection of pharmacological agents [Seeringer and Kirchheiner, 2008; Zhou *et al.* 2008].

Knowledge about the genetic predisposition to particular diseases will have to be available to both physicians and patients for effective use in disease prevention and screening. Predisposition-based screening should lead to earlier interventions, if diseases do occur. In RA, earlier diagnosis maximizes successful treatment and often reduces costs when compared to

a later diagnosis. Such practice will require new health policies as well as changes in the legal system since issues of concern are confidentiality, equitable access to valid tests, and proper utilization of resources.

We envision that the treatment of RA will not only include newer and more targeted agents but be truly personalized, based on the individual genetic, environmental and socioeconomic features related to drug response and toxicity. The realization of inexpensive, rapid methods of testing to accurately predict treatment responses in RA patients of different disease duration, race/ethnicity, and phenotypes, may not be on the horizon in the near future. However, the research to be performed to reach this goal will advance our understanding of the pathogenesis of RA. Identification of subsets of patients with optimal responses to different drugs may provide insights into different mechanisms of disease active in different patient subgroups.

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Conflict of interest statement

None declared.

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