Predicting Response to TNF Antagonists in Rheumatoid Arthritis
The Promise of Pharmacogenetics Research using Clinical Registries

Jeffrey D. Greenberg, M.D., M.P.H., and Harry Ostrer, M.D.

Abstract

Despite the demonstrated efficacy of three different classes of biologic response modifiers (BRMs) for the treatment of rheumatoid arthritis (RA), there are currently no clinical predictors or biomarkers that can rationally guide physicians in the selection of BRMs for individual patients. One promising area of translational research for patients with RA is the field of pharmacogenetics. In the absence of industry-sponsored pharmacogenetic studies of BRMs, longitudinal clinical registries may represent the most promising setting for identifying genetic biomarkers. This review focuses on published pharmacogenetic studies of TNF antagonists and discusses related methodologic issues for pharmacogenetic research using clinical registries.

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease associated with progressive disability, serious comorbidities, and increased mortality. The discovery and development of targeted biologic response modifiers (BRMs), particularly TNF antagonists, for the treatment of RA has dramatically changed the treatment paradigm and clinical outcomes for RA patients. However, 25% to 30% of RA patients do not respond to TNF antagonists, and serious adverse outcomes, including infections, have been associated with TNF antagonists. The identification of prognostic genetic biomarkers that can “personalize” the risks of drug toxicities, as well as predict the likelihood of clinical response to targeted BRMs, would represent a major advance for the treatment of RA.

The completion of the human genome sequencing project has represented a revolutionary advance in the field of human genetics. The simultaneous identification of large numbers of single nucleotide polymorphisms (SNPs), coupled with the development of rapid, high-throughput methods to genotype SNPs, has provided researchers with unprecedented tools for investigating the association of disease phenotypes with genotype biomarkers.

In the past decade, six biologic response modifier (BRM) agents targeting four different biologic targets have been approved by the Food and Drug Administration for the treatment of RA. Dozens of phase III and IV studies have been conducted using these agents. However, pharmacogenetic studies have only been conducted from one clinical trial of a single BRM. In the absence of industry-sponsored pharmacogenetic studies of BRMs, longitudinal observational registries may represent the most promising setting for identifying genetic biomarkers. This review will focus on published pharmacogenetic studies of TNF antagonists and discuss related methodologic issues for pharmacogenetic research using clinical registries.

Why Do We Need Genetic Biomarkers of Drug Response?

Although TNF antagonists have achieved unprecedented rates of clinical response in clinical trials of RA patients, there is consistent evidence that 25% to 30% of RA patients fail to respond. As a result, clinical trials of alternative biologic targets, including abatacept, a T cell costimulatory modulator, and rituximab, a B-cell depleting agent, have been conducted and demonstrated efficacy as well, including for patients who fail TNF antagonists. Despite the recent abundance of clinical trials demonstrating efficacy of different BRMs, evidence from head-to-head studies are generally lacking,
and the identification of biomarkers that could “personalize” a rational selection of BRM agent is needed.

Prior to the introduction of BRM agents, a number of studies investigated clinical predictors of response to traditional disease-modifying antirheumatic drugs (DMARDs). A recent systematic review of 28 studies noted that clinical variables, as well as HLA-DRB1 shared epitope (SE) status, failed to reliably predict response to traditional DMARDs in multiple studies.16 Similarly, studies of clinical predictors of response to TNF antagonists have failed to identify reproducible prognostic variables, with the exception of baseline joint count. In a study by Estrach and colleagues, the number of swollen joints at baseline was the only clinical variable found to predict response.17 In our work using the Consortium of Rheumatology Researchers of North America (CORRONA), we have also examined clinical predictors of response to TNF antagonists. In the CORRONA Registry, we observed that low baseline joint counts influence response, although floor effects may contribute to the attenuated response rates.18 Similarly, patients with lower baseline functional status have been observed to achieve less robust responses.19,20 With the exception of these disease activity measures, however, no demographic or clinical variables have been identified as predictors of response to TNF antagonists.

**Published Studies of TNF Antagonist Pharmacogenetics**

The identification of predictors of response and toxicity for RA patients prescribed BRM agents has been identified as a research priority in recent consensus statements.21,22 Prior to the introduction of TNF-α antagonists, pharmacogenetic studies had focused on genetic biomarkers of response to traditional DMARDs, including promising work on folate pathway SNPs for patients prescribed methotrexate.23,24 Since the introduction of TNF antagonists, an increasing number of pharmacogenetic studies have been pursued. Because of the specificity of the biologic target of TNF-α antagonists, TNF and TNF receptor polymorphisms have been the primary focus of investigations, along with other inflammatory cytokines. However, many of these studies have included small numbers of patients and single SNPs of candidate genes.

Only the TNF-α -308 G/A SNP has been replicated in multiple studies, although conflicting studies exist as well. Mugnier and associates reported that the -308 G/A polymorphism was associated with change in DAS-28 measurement in a study of 59 RA patients treated with infliximab.25 Similarly, Fonseca and colleagues observed that the same -308 G/A SNP of the TNF gene was associated with a decrease in DAS-28 for patients treated with infliximab.26 However, two other studies reported no association with response to infliximab for the -308 G/A SNP, including a study of 78 RA patients by Martinez and coworkers.27,28 Two additional studies found no association with the -308 G/A SNP as a single biomarker, but observed an association with response in an extended haplotype that included the -308 G/A SNP.9,29

Possible explanations for the conflicting nature of the study results include: 1. differences in biologic targets between etanercept and infliximab; 2. Type II error due to inadequate sample size; 3. Type I error due to chance and/or multiple comparisons; 4. population stratification; and 5. linkage disequilibrium between SNPs of candidate genes. No studies to date have examined genetic biomarkers of response to abatacept or rituximab.

**Why Are the Results of Published Pharmacogenetic Studies Inconsistent?**

Despite the promise of SNP markers in pharmacogenetics, the results of the TNF-α antagonist pharmacogenetic studies demonstrate the potential pitfalls and limitations of single SNP association studies. Genetic studies, in general, are susceptible to the same inconsistencies. A recent replication study of putative candidate gene associations with RA susceptibility in 4,027 individuals from the North American Rheumatoid Arthritis Consortium (NARAC) and a national Swedish RA registry found that only 3 of 17 putative candidate gene SNPs (PTPN22, PADI4 and CTLA4) were associated with RA susceptibility in a pooled analysis.20 These results indicate that previously reported negative results, particularly for the PADI4 and CTLA4 SNPs, were likely false negative (Type II) errors due to inadequate statistical power, linkage disequilibrium between adjacent SNPs, and/or population stratification. Similarly, it is likely that the earlier positive reports for the remaining 14 of 17 candidate SNPs were false positive (Type I) errors due to random chance, failure to account for multiple comparisons, linkage disequilibrium between adjacent SNPs, and/or population stratification.

In fact, racial and ethnic differences in allele frequencies have been demonstrated for a number of RA susceptibility genes, including SLC22A4, PTPN22 and TNF receptors, emphasizing the importance of genomic control methods to account for population stratification.31,32 Systemic differences in ancestry between cases and controls constitute population stratification, and can also lead to erroneous study conclusions.3,33 Genomic control methods using a panel of noncoding SNPs without any known association to the study phenotype can detect and adjust for differences in ancestry, although relatively few of the TNF-α pharmacogenetic studies have considered the effects of population stratification.33 To date, none of the TNF antagonist pharmacogenetic studies have accounted for the possibility of population stratification.

Concerns regarding the validity of single SNP findings in small association studies have been raised regarding the study results for other complex genetic diseases as well. Metaanalysis of published studies by Ioannidis and colleagues (370 studies) and Hirschhorn and associations (more than 600 studies) have confirmed that a minority of positive associations have been validated in replication association
studies. Specifically, population stratification and linkage disequilibrium have been cited as potential causes for non-replication in association studies. Linkage disequilibrium is defined as the nonrandom association of alleles from different genes (loci). Strong linkage disequilibrium has been demonstrated in many of the SNPs of inflammatory cytokines upregulated in RA patients, including the TNF-α, IL-1β and IL-6 genes, as well as chemokine and chemokine receptor genes. Moreover, the importance of noncoding SNPs has been underscored by recent discoveries, including the observation that multiple SNPs in high LD in a noncoding 3’ region of the CTLA-4 gene predisposed individuals to autoimmune diseases. These discoveries suggest that high density genotyping accounting for linkage disequilibrium may be the most promising approach, assuming that there is adequate statistical power.

The Promise of Clinical Databases for Pharmacogenetic Research

In the absence of adequately powered studies, poorly reproducible study results are inevitable. In the past decade, a number of large registries of patients prescribed TNF antagonists have been established in the United States and Europe. Although drug utilization, effectiveness, and pharmacovigilance may have been the primary motivations for establishments of these registries, the large cohorts of RA patients prescribed TNF antagonists and followed longitudinally represent well-characterized phenotypes for pharmacogenetics research. Until pharmaceutical companies conducting randomized controlled trials institute routine collection of DNA and conduct ancillary pharmacogenetic studies, large clinical databases that collect DNA samples will likely represent the most promising approach.

Conclusion

The identification of genetic biomarkers that can predict response and toxicities associated with targeted BRMs have been identified as a research priority in recent consensus statements. The recent identification of large numbers of SNPs, coupled with the development of rapid, cost-effective high-throughput methods, will facilitate pharmacogenetics research. Translational research registries that follow patients longitudinally represent a promising approach to advancing the field of pharmacogenetics research.

References

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