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Pharmacogenetics of Etanercept in Rheumatoid Arthritis

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Abstract

Etanercept is one of several TNF inhibitors approved for rheumatoid arthritis (RA) and a variety of other immune-mediated inflammatory conditions. Given the plethora of drugs approved for RA and the wide variations in cost and treatment response, markers of efficacy would be very useful. Several candidate genes, including HLA-DRB1 alleles and those encoding TNF, TNF receptors, and Fc receptors, have been examined for a role in the response to treatment with etanercept. In this review, we discuss pharmacogenetic studies of etanercept in RA and other diseases, and comment on the future of such analyses to advance the goal of personalized medicine in RA.

Treatment approaches to rheumatoid arthritis (RA) and related immune-mediated diseases have changed radically over the last 10 years. At present, there are six biologic agents approved by the US Food and Drug Administration for treatment of RA: three TNF inhibitors (etanercept, infliximab, adalimumab), a IL-1 receptor antagonist (anakinra); a CTLA4-Ig fusion protein (abatacept); and an anti-CD20 antibody (rituximab). Several other biologic agents are under development for treatment of RA, including the TNF inhibitors golimumab (1) and certolizumab (2) and an antibody directed against the IL-6 receptor, tocilizumab (3). Thus, predictors of drug responses among individual patients would be of great benefit by facilitating optimal choices of drug regimens at lowest cost and toxicity (4).

The basis for tests to predict treatment response or toxicity may include genetic polymorphisms, copy number variants, gene expression patterns in peripheral blood cells (or less likely synovium, which would require an invasive procedure), or proteomics on serum, plasma, or urine. Any or all of these would likely be interpreted in the context of clinical factors, such as serum rheumatoid factor or anti-CCP antibody, baseline disease severity, etc.

The TNF inhibitor etanercept (Enbrel®) is a fusion protein consisting of the TNF p75 receptor (TNFR2) and the CH2 domain, the CH3 domain and hinge region of human IgG (see Figure 1). Etanercept inhibits binding of both TNF- α and lymphotoxin alpha (LT α) to cell surface TNF receptors. Etanercept is approved for use in RA and a variety of other conditions (Table 1). For RA, etanercept is administered subcutaneously either once a week (50 mg) or twice a week (25 mg), and is generally very effective in reducing the signs and symptoms of RA, as well as structural damage and physical functioning (reviewed in (5)).

Pharmacogenetic studies of etanercept in RA

Pharmacogenetic studies of etanercept have been performed largely in RA. Candidate genes in which polymorphisms have been examined as markers of treatment response to etanercept

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in RA include: HLA-DRB1 alleles; tumor necrosis factor (*TNF*); lymphotoxin-alpha (*LTA*); interleukin-10 (*IL10*); transforming growth factor beta1 (*TGFB1*); IL1 receptor antagonist (*IL1RN*); TNF receptors (*TNFRSF1A* and *TNFRSF1B*); and Fc receptors (*FCGR2A*, *FCGR3A*, and *FCGR3B*). Padyukov et al. analyzed the role of 4 polymorphisms in *TNF*, *IL10*, *TGFB1*; and *IL1RN* in treatment response to etanercept in 123 patients with RA (6). Response rates were determined after three months using American College of Rheumatology 20% (ACR20) response criteria and disease activity score (DAS) 28 response criteria. Of 24 patients (20%) defined as non-responders, none of the alleles alone was significantly associated with response to treatment, although particular combinations of alleles in different genes were associated with good or poor responses to etanercept. For example, of 23 patients homozygous for both the *TNF*-308 G and *IL10*-1087 G alleles, 22 (96%) responded well according to ACR20 and DAS28 criteria. The combination of alleles in *IL1RN* (A2 allele corresponding to 2 copies of an 86 bp repeat in intron 2) and *TGFB1* (a rare C allele in codon 25) was associated with a less favorable treatment response. An additional link between responsiveness to etanercept in RA and *IL10* polymorphisms was reported by Schotte et al. (7). In their analysis, 50 patients were treated with etanercept alone for up to 4 years. *IL10* promoter microsatellite polymorphisms IL10.R and IL10.G were genotyped and haplotypes were deduced. A favorable treatment response was associated with the R3 allele or R3-G9 haplotype, whereas the allele G13 and the haplotype R2-G13 were predominant among patients with moderate or poor responses.

We have analyzed 457 patients with early RA who participated in a randomized controlled trial comparing weekly methotrexate and two doses of etanercept (10 mg and 25 mg twice weekly) (8). Based on the biologic pathway inhibited by etanercept (Figure 1), subjects were genotyped for HLA-DRB1 alleles and polymorphisms in the following genes: tumor necrosis factor (*TNF*), lymphotoxin alpha (*LTA*), TNF p55 and p75 receptors (*TNFRSF1A* and *TNFRSF1B*, respectively) and Fc receptors (*FCGR2A*, *FCGR3A*, and *FCGR3B*) (9). We found that the presence of two HLA-DRB1 alleles encoding the shared epitope (SE) (10) was associated with response to treatment with etanercept 25 mg twice weekly (odds ratio, OR = 4.3, 95% CI 1.8 - 10.3). Among Caucasians, two extended haplotypes that included the HLA-DRB1 alleles *0404 and *0101 (both of which encode the SE) and 6 single nucleotide polymorphisms (SNPs) in the *TNF-LTA* region (*0101-GGGAGG haplotype and *0404-GGAAGG) were associated with treatment response.

Kang et al. analyzed 13 SNPs within the *TNF* and *LTA* region for an association of clinical responses to 12 weeks of etanercept therapy among 70 patients with RA (11). In this study, the *TNF*-857 T allele was found to be marginally associated with a favorable treatment response. It should be noted that in the Korean population, the -308 A allele is very rare, perhaps explaining the failure to show an association of the -308 G allele with treatment response (12), as has been reported by Seitz et al. (13) and Guis et al. (14).

Pharmacogenetic studies of etanercept in other diseases

In their study, Seitz et al, analyzed the *TNF*-308 SNP for association with therapeutic response in RA (n=54), psoriatic arthritis (n=10), and ankylosing spondylitis (n=22). The majority of the 86 patients were treated with infliximab (n=63), while only 13 received etanercept. Moderate response across all disease groups was associated with the *TNF*-308 A/G genotype, whereas good response was exclusively seen in patients homozygous for the G allele. These results were confirmed in a recent study that looked at the influence of *TNF*-308 polymorphism in 86 RA patients from France treated with etanercept (14). Of these patients 21% had *TNF*-308 G/A genotype and 79% had *TNF*-308 G/G genotype. The patients' response to etanercept was assessed at 6 and 12 months using the DAS28. At both

these time points more patients with the G/G genotype had an improvement in DAS28 score than did patients with the G/A genotype.

Schmeling et al. (15) genotyped TNF –163, –238, –244, –308, and –376 SNPs in 137 juvenile inflammatory arthritis (JIA) patients treated with etanercept for at least 3 months and found that patients with the –308 GG genotype achieved an ACR-JRA 30 response after 6 months more frequently than patients with the genotype –308 G/A or A/A. In the subset of patients with rheumatoid factor negative polyarthritis, patients with the –308 G/G genotype achieved an ACR-JRA 30 response more frequently than those with the –308 G/A or A/A genotype (84 vs. 33% at 3 months, $P < 0.01$, 93 vs. 67% at 6 months, $P < 0.05$).

Tutuncu et al. (16) found that the functional –158 F/V polymorphism in the Fcγ receptor type IIIA gene (*FCGR3A*) correlated with clinical efficacy in RA patients and psoriatic arthritis patients treated with TNF inhibitors (infliximab, etanercept, and adalimumab). Among 35 patients (30 RA, 5 psoriatic arthritis), 23 were good responders, while 12 were non-responders. The low-affinity *FCGR3A* –158 F/F homozygous genotype was found to be significantly associated with response to TNF inhibitor therapy ($P < 0.01$ by Fisher's exact test). There was no association between the *FCGR3A* –158 SNP and etanercept response in an earlier study (8). Furthermore, this finding was not corroborated by Kastbom et al. (17), who studied 282 Swedish RA patients treated with TNF inhibitors after suboptimal responses to traditional DMARDs. They found no differences in *FCGR3A* –158 genotype distribution between non-responders and ACR20 responders, ACR50 responders, or ACR70 responders.

The future of pharmacogenetic studies of etanercept

There are many reasons for inconsistent findings of the association of various genetic variants with treatment response to etanercept and other therapeutic agents (18). The impact of differences in previous DMARD failures, baseline DMARD therapy, changes in DMARDs, or use of corticosteroids during the treatment period is often unclear. Many studies have a small number of subjects, which, leads to an increased likelihood of type II error. The definition for responders is highly variable, as is the treatment period. Often, subjects treated with different TNF inhibitors are analyzed together, which makes dissection of markers of responses to different TNF inhibitors problematic. In addition, results from subjects treated with etanercept for different diseases, such as RA or psoriatic arthritis, may be pooled, which raises uncertainty about the conclusions with regard to individual diseases.

The role of race/ethnicity is important in pharmacogenetic studies because the allele frequencies in the populations under study may vary. Some populations, particularly African-Americans, are recently admixed from one or more ancestral populations (19), which may influence results of pharmacogenetic studies and preclude the generalization of the results to other racial/ethnic groups.

There are many challenges to advancing the goal of personalized medicine through pharmacogenetics (20). Among them is the assembling of large, well-characterized groups of patients with standardized treatment regimens and outcome measures, with accompanying publicly available data and DNA samples. Large-scale genome-wide association studies on large groups of RA patients of defined phenotype, such as those of European ancestry with anti-CCP antibodies, have yielded novel insights into the pathogenesis of RA (21;22). With the assemblage of similar large groups of patients with data focused on treatment response, genome-wide studies to identify novel markers of treatment response to etanercept and other therapeutic agents will become a reality. If consistent markers of treatment response to etanercept are identified, a quick, reliable, clinically useful test can be developed. The goal

of personalized medicine, even if not fully realized, will lead to important improvements in our understanding of disease pathogenesis and patient care.

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Activated Macrophage

Figure 1. Interactions of TNF, LTA, TNFR1, and TNFR2

TNF is produced as a trimer on cell surface and cleaved by the enzyme TNF- α converting enzyme (TACE). TACE also cleaves TNF receptors, which are then soluble. TNF can bind to one of several TNF receptors, including TNFR1 and TNFR2. The TNF inhibitor etanercept is a fusion protein containing recombinant TNFR2 (hatched area) and a portion of the Fc region of human IgG₁. After binding to TNF or LTA, the etanercept protein is removed through the Fc receptor pathway.

Table 1**Clinical Indications for Use of Etanercept**

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- Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis (RA).
 - Reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients ages 2 and older.
 - Reducing signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function in patients with psoriatic arthritis.
 - Reducing signs and symptoms in patients with active ankylosing spondylitis.
 - Treatment of adult patients with chronic moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy.
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