Review Article

Pharmacogenetics: Reality or Dream in Predicting the Response to TNF-α Inhibitor Treatment?

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Abstract

Background: The ongoing progresses in the knowledge of the pathogenic mechanisms of various immune-mediated or inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, ankylosing spondylitis, disseminated granuloma annulare, psoriasis and/or psoriatic arthritis, and the availability of innovative biotechnological approaches have lead to the development of new drugs which add to conventional treatments. There are five TNF-α inhibitors available for clinical use including anti-TNF-α monoclonal antibodies (infliximab, adalimumab, golimumab and certolizumab pegol) and a fusion protein that acts as a "decoy receptor" for TNF-α (etanercept). Pharmacogenetics has the potential of increasing drug efficiency by identifying genetic factors responsible for lack response or toxicities to TNF-α inhibitors.

Methods: We analyzed the most recent studies in the literature relating to different genetic polymorphisms and their potential association with the therapeutic response to TNF-α inhibitors.

Results: SNP at position -308 of the TNF-α promoter genes and particularly the -308 G/G genotype and HLA-DRB1-encoding shared epitope (allele *0404 and allele *0101) may predict a better response to etanercept. Polymorphisms of TNFR1 and TNFR2 decrease response to infliximab. By contrast, FCGR3A-158 polymorphism seems to favor the response to infliximab. G allele of SNP rs610604 located in the TNFAIP3 gene and its haplotype with the T allele of rs2230926 could be considered as markers of good response to etanercept, infliximab and adalimumab.

Conclusion: Most of these studies are often small and not sufficiently powered to detect an effect and often examines only the effects of a single SNP, while it would be more useful to analyze more haplotypes in contemporary in the same patients. Candidate genes may be in linkage with other loci, thus, having a true influence upon the pharmacology of TNF-α inhibitors. Further studies are needed before a pharmacogenetic approach may be applicable in daily clinical therapeutic practice.

Keywords: TNF-α inhibitors; TNF-α gene polymorphisms

Introduction

During the last decade, many new biological immune modulators entered the market as new therapeutic principles. The ongoing progresses in the knowledge of the pathogenic mechanisms of various immune-mediated or inflammatory diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Crohn's disease (CD), ankylosing spondylitis (AS), disseminated granuloma annulare (DGA), psoriasis (Ps) and/or psoriatic arthritis (PsA), and the availability of innovative biotechnological approaches have lead to the development of new drugs which add to conventional treatments [1-7]. In particular, efforts have been made to design biologic drugs able to counteract the activity of different molecules such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, CD20, CD22 and CD11a. TNF-α is a pro-inflammatory cytokine known to a have a central role in the initial host response to infection and in the pathogenesis of the above-mentioned diseases [1-9]. TNF-α inhibitors have demonstrated efficacy in large, randomized controlled clinical trials either as monotherapy or in combination with other anti-inflammatory or disease-modifying anti-rheumatic drugs (DMARDs) in the treatment of chronic immune-mediated or inflammatory diseases [1-7,10,11]. There are five TNF-α inhibitors available for clinical use including anti-TNF-α monoclonal antibodies (mAbs) (infliximab, adalimumab, golimumab and certolizumab pegol) and a fusion protein that acts as a "decoy receptor" for TNF-α (etanercept) [1-7,12]. Furthermore, TNF-α inhibitors are able to reduce the expression and production of vascular endothelial growth factor (VEGF), nitric oxide (NO) and inducible NO synthase [12,13]. Notably, VEGF is a critical mediator of inflammation both in chronic immune-mediated and allergic diseases [14,15]. It is known that VEGF is a pro-angiogenic factor which alters the microvascular netwotk and, thus, correlates and may contribute to the development and progression of atherosclerosis. Etanercept and adalimumab may exert beneficial effects on the lipid profile improving the endothelial dysfunction [16]. In summary, the administration of TNF-α inhibitors reduces the systemic inflammation in patients with chronic immune-mediated diseases, improves both the clinical course of the disease itself and the endothelial function and, thus, may decrease the risk of acute cardiovascular and/or cerebrovascular events [12,17-19]. Finally, lymphotoxin (LT)-α seems to play a role in the development of flogosis of immune-mediated disease such as RA. Indeed, in RA, in addition to TNF-α, also LT-α expression in the synovium is elevated [20]. T-helper (Th)-1 and Th-17 lymphocytes have been associated with autoimmune diseases such as RA and expressed LT-α [21,22]. Depletion of LT-α–expressing Th-1 and Th-17 lymphocytes with LT-α–specific mAb may be beneficial in the treatment of autoimmune disease such as

RA [22]. However, it would seem that TNF-α inhibitors could bind LT-α as we have proven in PsA patients [23]. Although TNF-α inhibitors are generally well tolerated, physicians should be aware of the potential adverse events of these drugs [1-7]. Furthermore, high costs and concomitant immunosuppressive drugs favoring potential opportunistic infections decrease the prescription of TNF-α inhibitors. Pharmacogenetics has the potential of increasing drug efficiency by identifying genetic factors responsible for lack response or toxicities to TNF-α inhibitors [24]. In this paper, the authors will briefly review the biological roles of TNF-α in the pathogenesis of immune-mediated diseases and the potential role of pharmacogenetics in predicting the response to TNF-α inhibitors.

TNF-α: Structure and Biological Effects

TNF-α gene is located in the short arm of chromosome 6 in the MHC class III region between the HLA-B and HLA-DR genes. TNF-α was identified in 1975 as a factor isolated from the serum of endotoxin-treated mice able to induce the necrosis of a methylcholanthrene-induced murine sarcoma [8]. Thereafter, several members of the TNF and TNF-receptor (TNFR) superfamily were identified and it was demonstrated that this factors play an important role as regulators of immune cell proliferation, survival, differentiation, and apoptosis. TNF is first produced as a transmembrane protein (tmTNF), which then is cleaved by a metalloproteinase to a soluble form (sTNF) [9]. Biological activity results from the association of three monomers to form trimeric TNF, which then binds to cell-surface TNFR1 or TNFR2, leading to receptor oligomerisation. Both TNFR1 and TNFR2 can deliver signals through anti-apoptotic and pro-inflammatory pathways [9]. Moreover, TNFR1 is necessary for defense against bacterial infection, whereas TNFR2 might have a role in downregulating TNF-driven inflammatory signals. TNF-α favors the recruitment and the activation of lymphocytes, neutrophils and platelets, the expression of adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1) and E-selectin on endothelial cells and induces the neo-angiogenesis in the sites of flogosis. TNF has a central role in the initial host response to infection [25]. In tuberculosis, it results in macrophage activation, cell recruitment, granuloma formation, and maintenance of granuloma integrity [26]. Mice lacking the gene for TNF or TNFR1, or treated with an anti-TNF monoclonal antibody, fail to contain the infection after challenge with *Mycobacterium tuberculosis* [27]. Other studies have implicated TNF, TNFR1, and TNFR2 as being important in murine defense against other intracellular pathogens such as *Listeria monocytogenes* and *Salmonella typhimurium* [28,29]. TNF-α is produced mainly by activated macrophages in the inflamed synovial membrane tissue and induces the production of other pro-inflammatory cytokines, including IL-1 and IL-6, together with the production and release of chemokines (i.e. IL-8, Rantes) that attract leukocytes from the blood into the inflamed tissue. This process is facilitated by the upregulation on endothelium of integrins and adhesion molecules, including E-selectin and VCAM-1. Finally, the destruction of the underlying articular cartilage and subchondral bone is initiated by the induction of proteolytic and metalloproteinase enzymes [30].

Pharmacogenetics

Although TNF-α inhibitors have demonstrated to be effective in the treatment of patients with immune-mediated or inflammatory diseases, a substantial proportion of the patients fall to achieve a satisfactory clinical response. However, determinant for drug efficacy and toxicity are still largely unknown. Therefore, identifying the patients who will benefit from TNF-α inhibitors remains a lottery [31-35]. Pharmacogenetics holds the promise not only to explain inter-individual variability in drug response, but also to predict efficacy and adverse drug events. Several studies have gathered considerable information on drug interaction with TNF-α. Despite genetic susceptibility markers such as the shared epitope (SE), recognition that variation in response to the treatment TNF-α inhibitors may be linked to genetic traits led to the study of genetic markers as potential predictors of response to the treatment. Such analyses provide a step towards using genetics in a fully translational approach, from both a screening and therapeutic response perspective, to informing clinical practice. Genes encoding proteins involved in the immune response continue to be studied to determine whether they are robust markers to predict the response to TNF-α inhibitors. However, several genetic variants have been analyzed in the TNF-LTα region. The TNF gene loci are obvious candidates for influencing the response to TNF-α inhibitors. Several polymorphic regions of the TNF locus have been identified and studied, including single nucleotide polymorphisms (SNPs) at position -308, -238 and -857 of the TNF promoter genes and -676 and -196 of the TNF receptor genes [36]. The SNP at position -308 represents the best studied potential genetic marker for response to TNF-α inhibitors. Polymorphism at position -308 of the TNF-α gene is known to influence binding of transcription factors and to control the level of TNF-α production [37]. Louis et al. [38] genotyped CD patients for the TNF-α -308 A/G polymorphism and compared the response rates after infliximab therapy. No significant difference between response groups could be demonstrated. Mascheretti et al. [39] analyzed SNPs in the TNF-α, TNFR1 and TNFR2 in two cohorts of patients with active CD (90 and 444 patients, respectively from the ACCENT I study) who were treated with infliximab. Only the homozygous mutant G-allele at position TNFR2 +587 seemed to predict a worse treatment outcome to infliximab in the small cohort of patients. On the contrary, Pierik et al. [40] reported the association between the TNFR1 +36 polymorphism and a decrease response to infliximab in patients with inflammatory bowel disease. Urcelay et al. [41] showed an association between a genetic polymorphism located in the 5q31 locus containing the IBD5 gene and a lack of response to infliximab. Guis et al. [42] have investigated the influence of -308 A/G polymorphism upon the response to etanercept in 86 patients with RA. The study demonstrated that the patients with the -308 G/G genotype presented a better response to etanercept than those with -308 A/G genotype after 1 year of treatment. Moreover, TNF-α polymorphism associated with elevated levels of TNF-α is also associated with poor response to TNF-α inhibitors. Maxweel et al. [43] studied 1050 patients with RA: 455 were treated with etanercept and 450 with infliximab. They demonstrated that the TNF-α -308A/A genotype was associated with a significantly poorer response to etanercept. There was no association between the -308 genotype and the response to infliximab. These findings raise important questions about the mechanistic differences between etanercept and infliximab and the potential for genotype to influence the response to treatment. Notably, etanercept, uniquely among the TNF-α inhibitors, binds LT-α [23] and does so with similar affinity to soluble TNF-α. It has been reported that in patients with inflammatory bowel disease, LT-α synthesis can be influenced by genotype at -308 positions. In particular, the A/A genotype favors a higher secretion of LT-α. It is possible that in presence of elevated quantities of TNF-α and LT-α in patients with the TNF-α -308 A/A genotype, the potency of etanercept may not be able to neutralize both cytokines with the consequent reduced response to etanercept. Schmeling and Horneff [44] also confirmed in 137 patients with juvenile idiopathic arthritis treated with etanercept that the TNF-α

-308A/A genotype decreases the response to etanercept treatment. Marotte et al. [45] investigated the association between the TNF-α -308 gene polymorphism and the circulating level of bioactive TNF-α in 198 patients with RA. The authors reported that the circulating level of bioactive TNF-α resulted higher in patients carrying the TNF-α -308 A/A or A/G genotype. However, the circulating level of bioactive TNF-α could not be calculated as free TNF-α and, thus, many other factors might play a role. Indeed, IL-1, IL-6 and IL-17 act through synergistic interactions with TNF-α. Furthermore, both this study and that of Cuchacovisch et al. [46] confirmed no association between the -308 genotype and the response to infliximab. By contrast, Mugnier et al. [47] and Fonseca et al. [48] reported a positive association of clinical effect with the TNF-α G/G genotype. The potential role of HLA-DRB1 shared epitope was investigated in two studies [49,50] in predicting infliximab response, showing no positive correlation with response to therapy. Padyukov et al. [51] reported that TNF-α -308 G/G and IL-10-1087G/G favor the response to etanercept in patients with RA. However, potential other genetic polymorphism may affect the therapeutic response. Indeed, the -857 C/T SNP, which is also located in the promoter region of the TNF-α, seems to favor the response to etanercept [52]. Moreover, the IL-10 promotor microsatellite allele IL-10.R3 and the haplotype R3-G9 were demonstrated to be associate with positive response to etanercept. Criswell et al. [53] found that patients with RA who had 2 copies of the HLA-DRB1-encoding SE (allele *0404 and allele *0101) were significantly more likely to respond to etanercept treatment, while genes in the TNF-LTα region did not appear to be related to therapy response. Of note, HLA-DRB1 SE alleles predispose to anti–citrullinated protein antibody (ACPA)-positive RA [54]. Soto et al. [55] investigated the potential associations between ACPA and response to adalimumab therapy in patients with RA. The authors reported that the patients carrying -308 TNF-α G/G genotype displayed a better response to adalimumab. However, they showed that the presence of ACPA did not affect the response to adalimumab in -308 TNF-α G/G genotype patient. Another study demonstrated that the polymorphisms in NOD2, CD14 and Toll-like receptor (TLR) 4 genes did not influence the response to adalimumab in patients with CD [56]. However, Potter et al. [57] reported that several SNPs mapping to the TLR and NFκB as MyD88 and CHUK were associated with the response particularly to etanercept. Furthermore, the functional polymorphism 676 T>G in the TNF super family 1b gene was not also associated with the response to infliximab and adalimumab in patients with RA [58]. The role of IL-6 in the pathogenesis of RA is supported by several studies [59,60]. Jančič´ et al. [61] investigated whether -174 G/G IL-6 gene polymorphism, which was correlated with IL-6 level, could influence the clinical response to etanercept in patients with RA. The authors demonstrated that -174 G/G IL-6 gene polymorphism enhances the response to etanercept. FCGR3A is another polymorphism which has been investigated. FCGR3A gene encodes FcγRIIIa (CD16) which is expressed on macrophages, monocytes and natural killer (NK) cells. Moroi et al. [62] have demonstrated in patients with CD that the FCGR3A-158 polymorphism affects the infliximab-binding affinity of NK cells and infliximab-mediated antibody-dependent cell-mediated cytotoxicity activity, thus favoring the biological response to infliximab. TNFAIP3 gene has been associated with Ps, RA, SLE, type-1 diabetes mellitus and celiac disease. It has been demonstrated that the G allele of SNP rs610604 located in the TNFAIP3 gene and its haplotype with the T allele of rs2230926 could be considered as markers of good response to etanercept, infliximab and adalimumab therapy in patients with Ps [63]. Furthermore, p38 mitogen-activated protein kinases (MAPK) have been considered to play a role in the pathogenesis of RA, including production of pro-inflammatory cytokines. More SNPs in genes from

every level of the p38 MAPK cascade have been associated with the response to TNF-α inhibitors, particularly with infliximab and adalimumab [64]. However, infliximab and adalimumab have a greater ability to stimulate reverse signaling through binding TNF-α on the cell surface. It is conceivable that this type of signaling may involve some components of the p38 MAPK network, and, thus, variants of the gene could alter the degree of signaling [64]. Another study revealed that the G allele at rs10865035 mapping to AFF3 favored the response to etanercept, infliximab and adalimumab in patients with RA, while, at the CD226, the SNP rs763361 C allele decreased the clinical response to treatment [65]. Finally, may of the RA risk alleles are near genes involved in TNF-α signaling, including PTPRC/CD45 [66]. Cui et al. [66] demonstrated that PTPRC/CD45 favored a clinical response to TNF-α inhibitors treatment in RA patients, especially among those having ACPA or rheumatoid factor (RF). Khanna et al. [67] reported an association between the TNFA –308 polymorphism and progression of radiographic damage in patients with early seropositive RA. This association appeared to be independent of the SE, but might be dependent on other genetic variants in linkage disequilibrium with the –308 TNFA A allele and DRB1*0301. By contrast, Reneses et al. [68] reported that erosive damage at 1 year in patients with recent-onset RA is significantly influenced by HLA-DRB1 SE homozygosity, but not by RF, ACPA and 308 TNF-alpha genotype. However, both Khanna et al. [67] and Reneses et al. [68] did not investigate potential influence of this polymorphism upon the response to TNF-α inhibitors.

In table 1 are reported the potential association between genetic polymorphisms and response to TNF-α inhibitors.

Conclusion

TNF-α inhibitors have been demonstrated to be effective in the treatment of immune-mediated or inflammatory diseases such as RA, SLE, CD, AS, DGA, Ps and/or PsA. Although TNF-α inhibitors are generally well tolerated, physicians should be aware of the potential adverse events of these drugs. There is an increasing need for an individualized therapy strategy guided by predictors of response. Several studies have reported associations between genetic polymorphisms and drug efficient response. A few studies seem to demonstrate that the SNP at position -308 of the TNF-α promoter genes and particularly the -308 G/G genotype may predict a better response to etanercept than those with -308 A/G and A/A genotypes. HLA-DRB1-encoding shared epitope (allele *0404 and allele *0101) also seems to favor a better clinical outcome in patients treated with etanercept. It is possible that high levels of LT-α may affect the therapeutic response. Other studies have analyzed polymorphisms of TNFR1 and TNFR2 that decrease response to infliximab. It is possible that the poorer response to treatment may depend on the more severe disease activity. HLA-DRB1 and -174 G/G IL-6 gene polymorphism seem also to favor the response to etanercept. By contrast, FCGR3A-158 polymorphism seems to favor the response to infliximab. However, most of these studies are often small and not sufficiently powered to detect an effect and markers tend to be more prognostic than predictive of therapeutic response. Furthermore, studies often examine only the effects of a single SNP, while it would be more useful to analyze more haplotypes in contemporary in the same patients. Candidate genes may be in linkage with other loci, thus, having a true influence upon the pharmacology of TNF-α inhibitors. Difficulties also arise when genetic variants are disease related such as HLA-DRB1 which is associated with more severe RA disease activity. Finally, in pharmacogenetic studies, it is important that baseline characteristics and drug dosages between cohorts are kept at similar level to estimate adequately associations between genetic

Author	Polymorphism	Disease	Drug investigated	Response to drug
Louis et al. [37]	TNF-α -308 A/G	CD	Infliximab	No influence
Mascheretti et al. [39]	Homozygous mutant G-allele at position TNFR2 +587	CD	Infliximab	Worse response
Pierik et al. [40]	TNFR1 +36	Inflammatory bowel disease	Infliximab	Worse response
Urcelay et al. [41]	IBD5 polymorphisms	Inflammatory bowel disease	Infliximab	Lack of response
Guis et al. [42]	TNF-α -308 G/G genotype	RA	Etanercept	Better response
Maxwell et al. [43]	TNF-α -308 A/A genotype	RA	Etanercept	Worse response
Schmeling and Horneff [44]	TNF-α -308 A/A genotype	juvenile idiopathic arthritis	Etanercept	Worse response
Cuchacovich et al. [46]	TNF-α -308 genotype	RA	Infliximab	No influence
Mugnier et al. [47]	TNF-α -308 G/G genotype	RA	Infliximab	Better response
Fonseca et al. [48]	TNF-α -308 G/G genotype	RA	Infliximab	Better response
Padyukov et al. [51]	TNF-α -308 G/G IL-10-1087G/G	RA	Etanercept	Better response
Kang et al. [52]	TNF-α -857 C/T	RA	Etanercept	Better response
Criswell et al. [53]	HLA-DRB1*0404 and *0101	RA	Etanercept	Better response
Soto et al. [55]	TNF-α -308 TNF-α G/G genotype	RA	Adalimumab	Better response
Barreiro-de Acosta et al. [56]	NOD2, CD14, TLR4	CD	Adalimumab	No influence
Potter et al. [57]	TLR and NFκB, MyD88 and CHUK		Etanercept	Better response
Jancic et al. [61]	-174 G/G IL-6 gene polymorphism	RA	Etanercept	Better response
Tejasvi et al. [63]	G allele of SNP rs610604 and T allele of SNP rs2230926 in TNFAIP3	Ps	Etanercept, infliximab, adalimumab	Better response
Tan et al. [65]	G allele at rs10865035 in AFF3	RA	Etanercept, infliximab, adalimumab	Better response

Table 1: Potential Association between Genetic Polymorphisms and Response to TNF-α Inhibitors.

polymorphisms and treatment response. In conclusion, further studies are needed before a pharmacogenetic approach may be applicable in daily clinical therapeutic practice.

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