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REVIEW ARTICLE

Clinical parameters and biomarkers for anti-TNF treatment prognosis in rheumatoid arthritis patients

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Abstract Tumor necrosis factor (TNF) plays a pivotal role in the pathogenesis of rheumatoid arthritis (RA). This finding has led to the development of TNF blockers for RA treatment. However, response to these therapies is heterogeneous with success in only two thirds of patient. Some clinical aspects useful in the attempt to predict the response to TNF inhibitors is the promptness and the magnitude of the response at the first weeks and a low basal disease activity, while comorbidities, tobacco, glucocorticoids treatment, and high basal radiological score correlate with a poorer response. The role of TNF promoter polymorphisms in clinical response to anti-TNF therapies is controversial. A correlation between the presence of high baseline titers of rheumatoid factor (RF) and decreased response to anti-TNF treatment has been reported. Most studies show decreased RF titers during anti-TNF treatment mainly in patients who responded to treatment. There is no consensus about the usefulness of basal anti-citrullinated protein antibodies (ACPA) levels, and a decrease in ACPA titers as predictor of clinical response to anti-TNF therapy. Despite some promising markers identified to fulfill this role, currently the predictive value of single markers seems not strong enough to predict treatment response in an individual RA patient.

Keywords Anti-TNF · Cytokines · Polymorphisms · Rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disease that mainly affects synovial joints and periarticular tissue, destroying both cartilage and bone. Recently, knowledge about its pathogenesis has increased, especially on the proinflammatory role of cytokines. However, its etiology is still unknown. Studies done on patients seropositive to rheumatoid factor (RF), an autoantibody against the Fc fragment of IgG, suggest a key role of immune complexes that accumulate in synovial joints activating the complement cascade and Fc receptors. These lead to chronic synovitis with an increase of inflammatory cell activity and proinflammatory cytokine levels such as tumor necrosis factor (TNF) and interleukin (IL)-1. Nevertheless, not all patients are seropositive for RF, suggesting that RA is a common phenotype for several different disorders.

Although TNF, which binds to two receptors (TNFR-I and TNFR-II), has several beneficial effects, including increased microorganism clearance, decreased mitosis rate, stimulation of apoptosis, and increased expression of cell adhesion molecules and chemokines [1], several studies established that

synovium from RA patients secrete elevated levels of TNF [2]. In addition, mice overexpressing this cytokine present a rheumatoid arthritis-like disease.

Due to the key role of TNF in RA, drugs that inhibit its effects have been developed, such as infliximab, a chimeric monoclonal antibody; adalimumab, a fully human monoclonal antibody; and etanercept, a soluble TNF receptor formed by a ligand recognition segment of the human TNFR-II and the Fc fragment of human IgG1. Furthermore, it is well known that anti-TNF antibodies decrease the levels of IL-1, IL-6, adhesion molecules and chemokines, among other molecules [2, 3]. Also, the number of swollen joints and its cellular infiltration decrease, as well as the rate of destruction of cartilage and bone after anti-TNF drugs treatment [4].

Although the development of these new treatments are among the most effective therapies for RA, they have some disadvantages: not all patients respond, anti-TNF treatments have serious potential adverse effects (infection, cancer, etc.) and high cost. Hence, recognizing clinical and biological predictors of treatment response is important in order to enable early identification of patients who will benefit from this therapy [5].

Clinical response predictors

The RA activity and the degree of joint damage are critical in the evolution of the dysfunction. They had been measured by objective instruments, like the American College of Rheumatism (ACR) response criteria and the disease activity score for 28 joints (DAS28). The ACR criteria measure the difference between two evaluation moments in a patient using joint assessment, patient and physician global assessment, and the health assessment questionnaire (HAQ). The DAS score shows the disease state in one moment using a formula that include 28 joints count, a patient global assessment and an inflammation factor as erythrocyte sedimentation rate (ESR) or C reactive protein (CRP). These tools are different because while ACR 20, 50, and 70 response criteria can assess the damage gain on time, the DAS28 shows the inflammation change and this factor could be modified faster than the ACR response.

When a physician evaluates a patient for the first time, the ideal would be to have a clinical and demographic approach that could predict an optimal response to the anti-TNF treatment, hence the importance of having reliable quantifying instruments to support the medical assessment.

Depending on the mechanism of action of biologic drugs, some predictor factors have been identified. Some clinical aspects useful in the attempt to predict the response to anti-TNF inhibitors is the promptness and the magnitude of the response at the first weeks of therapy, as demonstrated by the OPTIMA [6], RAPID [7], and ATTRACT trials [8]. Moreover, the ATTRACT study demonstrated that those patients who had the greatest decrease in CRP levels had the best response to anti TNF therapy.

Both HAQ and DAS28 have demonstrated their usefulness as predictive response factors to anti-TNF treatment, as established in the TEMPO [9] and ReAct [10] studies. The results indicated that a value of DAS28 greater than 7.1 and a HAQ over 1.5 were associated with a decreased likelihood of responding to treatment, while a DAS28 lower than 4 was associated to a better response to treatment.

TEMPO [9] and ReAct [10] studies had also shown that the young male patients have a better remission probability, while comorbidities, tobacco, glucocorticoids treatment, high global assessment, disease age older than 65, and a long evolution time have been associated to a poor response to these drugs (Table 1).

One of the most critical objectives in the trials that determine the responsiveness to biological therapy is the radiological change measurement by the Sharp Van der Heijde modified score that measure the disease progression by the joint space narrowing and the erosion presence, and can show better the level of disease in spite of the clinical parameters improvement. The TEMPO study showed that the probability of achieving remission is inversely correlated with the baseline Sharp score [11]. Another way to evaluate the disease progression is using the rapid radiologic progression (RRP). In a set of early RA population at the BeSt and ASPIRE trials, authors have found that baseline CRP, ESR, swollen joint count (out of 28 joints), and presence of RF are good response predictors to TNF inhibitors in order to avoid RRP [12, 13]. In addition, Visser et al. [14] found that RRP occurred, in particular, in patients who had started treatment with methotrexate (MTX) monotherapy, rather than those who started with initial combination therapy including MTX and either prednisone or infliximab.

Another relevant clinical aspect to be considered when predicting good response to anti-TNF drugs is the concurrent use of MTX, as have been demonstrated by the TEMPO trial. In this regard, the response to certain drugs has been related to anti-drugs antibodies, and it is thought that their production can be inhibited by MTX [15]. Even though any biologic drug can induce this kind of immunogenicity, the propensity depends mainly on the specific agent [16]. These antibodies are able to reduce the TNF inhibitors therapeutic effect, modifying the drug pharmacokinetics or neutralizing it [17]. This phenomenon may cause not only a different response rate between each TNF inhibitor, but also imply different dose escalation, and reduction in sustainable efficacy and repeatable efficacy. An interesting mechanism to explain the role of anti-drug antibodies in responsiveness to anti-TNF is the fact that there exist an inverse correlation between high levels of these antibodies and lower mean serum drug concentration [18].

Table 1 TNFi good responders clinical predictors

Study	TNFi	Good response likelihood	Poor response likelihood
ReAct (10)	ADA	Age younger 40	Age older 65
		Gender, male	Tobacco
			Glucocorticoids
			Higher basal DAS28 (7.1)
			Higher HAQ (>1.5)
			High PGAD
TEMPO (9)	ETA	Gender, male	
RAPID (6)	CTZ	Short time to response	
OPTIMA (5)	ADA	Short time to response	
ATTRACT (7)	INF	RCP decrease	

ADA adalimumab, *ETA* etanercept, *CTZ* certolizumab, *INF* infliximab, *PGAD* patient assessment global disease, *RCP* reactive C protein

TNF levels

Recent studies have tried to determine the association between TNF serum levels and therapeutic response. Findings from our group demonstrated a positive correlation between TNF levels and clinical response with infliximab [19] and adalimumab [20]. In our first study with twenty patients, TNF levels increased significantly with respect to basal levels in most patients after infliximab treatment. However, only a subgroup of patients, those with −308 G/A polymorphism on the TNF gene promoter, showed a significant correlation between ACR 50 criteria of improvement and an increase of TNF levels [19]. The second study showed that when comparing baseline TNF levels to those achieved at 8, 16, and 24 weeks of adalimumab treatment, only responder patients showed a statistically significant overall increase in TNF concentration over time [20]. Marotte et al. evaluated circulating TNF bioactivity, demonstrating that levels of bioactivity were predictive of clinical response to infliximab [21, 22] (Table 2).

Two other studies showed discordant results related to TNF levels in synovial tissue, with no clear conclusions. Wijbrandts et al. investigated in one hundred and fifty-eight patients with RA, whether immunohistological assessment of cell infiltrate and cytokine expression in the synovium prior to initiation of anti-TNF treatment could predict clinical response. They found that TNF levels were higher in the synovial sublining layer of responders to anti-TNF therapy when compared to nonresponders [23]. Similarly, TNF expression in the intimal lining layer was higher in responders as compared to nonresponders. Buch et al. had contrasting results with fifty-one patients who had arthroscopic biopsies of the knee joint prior to infliximab treatment. Pretreatment synovial TNF expression did not predict a TNF blockade response, and both, ACR response and nonresponse, showed reduction in synovial TNF levels [24].

Table 2 Basal TNF levels and basal TNF bioactivity, as predictors of clinical response

Authors [reference]	Assesment: evaluation criteria	No. of patients	TNF blockers	Response
Cuchacovich et al. [19] (TNF levels)	ACR	20	IFN	NC
Cuchacovich et al. [20] (TNF levels)	DAS 28	81	ADA	NC[a]
Marotte et al. [21] (TNF bioactivity)	ACR	42	IFN	C
Marotte et al. [22] (TNF bioactivity)	ACR	50	IFN	C
Wijbrandts et al.[23] (TNF expression in synovial tissue)	DAS 28	143	IFN	C
Buch et al. [24] (TNF expression in synovial tissue)	ACR	51	IFN	NC

ACR American College of Rheumatism (ACR) response criteria, *DAS28* disease activity score for 28 joints, *IFN* infliximab, *ADA* adalimumab, *NC* no correlation, *C* correlation

[a] However, responder patients showed a significant overall increase in TNF concentration over time.

TNF gene polymorphisms

The −308 G/A polymorphism on the TNF gene promoter region has been extensively studied and associated with higher TNF production [25, 26]. This had led to evaluate −308 G/A genotype as a predictor of anti-TNF treatment response. Some studies found that the presence of this genotype in infliximab- [27–29], etanercept- [29–31], and adalimumab-treated patients [20, 29] was a poor response predictor. Most of these studies were done with a limited cohort ($n<100$), as opposed to those done with higher number, that presented contradictory results [22, 32, 33]. Furthermore, two recent meta-analyses failed to prove that −308 G/A genotype, neither in heterozygous or homozygous condition, is associated to a poor response to anti-TNF drugs treatment [34, 35]. However, none of these meta-analyses evaluated the studies according to the main clinical outcome used. ACR criteria are a measure of change, while DAS28 index is an absolute measure of disease activity and a continuous variable. Both measures are useful to discriminate between a drug and a placebo, but when drugs become more effective, the ACR criteria could underestimate improvement. In these two meta-analyses, thirteen studies were selected (both of them included similar studies). When we analyzed the characteristics of the studies included in Pavy et al. meta-analysis [35], we found that three studies (1,035 patients) used the ACR criteria for improvement and none of them showed a relationship between −308 G/A polymorphism and responsiveness to anti-TNF treatment. Ten studies used the DAS28 index (2,072 patients). Six of these studies (686 patients) found a correlation between the −308 G/A polymorphism and clinical response to anti-TNF treatment. One study from Padyukov et al., also using the DAS28 index, did not find a significant association between −308 G/A polymorphism and response to treatment. However, a certain combination of alleles (−308 G/G and −1087 G/G) was linked to good response to etanercept. We have studied the influence of the -308 TNF G/A polymorphism on the clinical response to infliximab in a cohort of eighty-one RA patients [19]. We found a significantly higher percentage of DAS28 responders in the G/G group versus the G/A group. Patients from the G/G group also showed a significantly higher DAS28 improvement. Although we found a significant difference when DAS28 was used, no differences were found between groups with the ACR improvement criteria. Hence, we suggest that even the evidence is weak, more prospective studies using the DAS28 index should be made to clarify this matter. It is worth mentioning that most of these studies were performed with European patients, except for ours [19], which was performed with Chilean patients. However, the disparity of treatment response evaluation criteria in different studies, and different genetic backgrounds could hinder comparison between different studies (Table 3).

Regarding the association between another TNF gene polymorphism, −238 G/A, and anti-TNF responsiveness, there is limited evidence. To date, two studies with infliximab have showed contradictory results. Maxwell et al. reported that TNF −238 G/A genotype was associated with a poorer response to infliximab [32]; however, Fabris et al. [36] reported that the −238 G/A genotype was absent in severe unresponsive RA, but present in mild-responsive RA subjects. They concluded that −238 G/G homozygosis associates with severity and unresponsiveness. No association with responsiveness was found in a study with etanercept [32]. Recently, a meta-analysis has confirmed an association between −238 A allele and poor response to infliximab therapy [34]. Nevertheless, more research is necessary to establish the role of this polymorphism as a marker for response to anti-TNF agents in RA.

Anti-citrullinated protein antibodies and RF

Currently, the main outcome in RA therapy is disease remission. Given that minimal joint damage is produced in subclinical stages, early diagnosis is required to accomplish a good response. In this context, RF and anti-citrullinated protein antibodies (ACPAs) have emerged as early disease markers. These antibodies have high specificity, but ACPAs has higher sensitivity [37]. Moreover, it is recognized that a large amount of RA patients have positive antibody titers prior to clinical manifestations. This constitutes a high risk of disease development [38]. Also, high ACPA levels are correlated with more severe pathology, which adds a severity predictor value to it [39]. Interestingly, it has been observed that treatment with some drugs, particularly MTX and anti-TNF, changes serum ACPA and RF levels [40, 41]. Current research seeks for an association between response to treatment and basal antibody levels or antibody levels during therapy; however, there is only one meta-analysis on this topic.

1. Basal RF levels and response to anti-TNF treatment

   Bobbio-Pallavicini et al. have reported that basal high IgA-RF levels were associated with poor clinical response to infliximab treatment [41]. Similarly, de Rycke et al. reported that baseline IgM-RF levels correlated inversely with changes in CRP and ESR during infliximab treatment [42]. Patients with high baseline IgM-RF levels had a less pronounced decrease in acute phase reactants during treatment. In contrast, Onishi et al. did not find a correlation between basal IgM-RF levels and clinical response to infliximab therapy [43]. Potter et al. reported that patients positive for RF demonstrated significantly less improvement in their DAS28 values than RF negative patients, following infliximab or etanercept therapy [31].

   Bobbio-Pallavicini et al. reported that high IgA-RF levels were associated with poor clinical response to

etanercept or to adalimumab treatment [41]. Lv et al. recently published a meta-analysis studying the predictive effect of the RF status for patient response, suggesting that the RF status was not associated with patients' response to anti-TNF treatment, with a moderate heterogeneity observed. However, this study did not analyze the baseline RF levels [44].

Concisely, most studies demonstrate an association between the presence of high baseline titers of RF and reduced response to anti-TNF treatment.

2. Basal ACPA levels and response to anti-TNF treatment

De Rycke et al. reported that baseline concentrations of ACPAs did not correlate significantly with changes in CRP or ESR during infliximab treatment [42]. Onishi et al. did not find correlation between basal ACPA levels and clinical response to infliximab treatment [43]. Potter et al. reported that patients positive for ACPAs had significantly less improvement in DAS28 compared to ACPA negative subjects, during infliximab or etanercept treatment [31]. Our group has reported that basal ACPA levels predict a better clinical response to adalimumab treatment [45]. Lv et al. recently published a meta-analysis studying for an association of ACPA antibody status and patient response to anti-TNF treatment. The overall meta-analysis showed no association between the status of ACPA antibody and patients' response to anti-TNF treatment [44]. Briefly, there is no consensus about the usefulness of basal ACPA levels as a predictor of clinical response to anti-TNF therapy.

3. RF levels evolution during anti-TNF treatment

Bobbio-Pallavicini et al. found a significant reduction in RF levels on time during infliximab treatment, for all RF isotypes, in the responder group of patients [41]. Similarly, de Rycke et al. reported that IgM-RF levels were reduced significantly during infliximab treatment for the whole group of patients. [42]. Alessandri et al. reported that a significant decrease in serum RF was observed only in patients who had clinical improvement during infliximab treatment [46]. Onishi et al. reported a significant decrease in IgM-RF levels on time, only in the group of responder patients [43].

Bobbio-Pallavicini et al. reported that a significant reduction in RF levels was observed for all RF-isotypes in the responder group of patients during etanercept treatment [41]. Chen et al. reported that etanercept treatment induced a significant decrease in serum IgM-RF levels [47]. In contrast, Onishi et al. did not find a significant decrease in IgM-RF levels on time for both groups of responder or nonresponder patients during etanercept treatment [43].

Bobbio-Pallavicini et al. reported that a significant reduction in RF levels was observed for all RF isotypes in the responder group of patients during adalimumab treatment [41]. Atzeni et al. studied fifty-seven RA patients and reported that adalimumab treatment induced a significant decrease in IgM-RF levels, and the decrease in antibody titers correlated with the clinical response to therapy [48]. Bos et al. reported a significant decline in IgM-RF levels, mainly in the responder group of patients to adalimumab treatment [49]. Our group has found that RF titers exhibited a progressive and significant reduction from baseline to 8, 16, and 24 weeks for all patients during adalimumab treatment [45].

To sum up, most studies show decreased RF titers during anti-TNF treatment, mainly in patients who responded to treatment.

4. Course of ACPA levels during anti TNF treatment

Bobbio-Pallavicini et al. reported that ACPAs titers do not decrease during infliximab treatment [41]. Alessandri et al. reported that a significant decrease in serum ACPAs was observed only in patients who had clinical improvement during infliximab treatment [46]. De Ryke et al. compared the concentrations of ACPAs at baseline and after 30 weeks of infliximab treatment. No significant differences were found, suggesting that ACPAs are not modulated by infliximab treatment [42]. Onishi et al. reported a significant decrease in ACPA levels on time only in the group of responder patients to infliximab [43].

Bobbio-Pallavicini et al. reported that ACPA levels do not decrease during etanercept treatment [41]. Chen et al. reported that serum ACPA levels decreased significantly after a 3-month course of etanercept treatment. The variation in ACPA levels was positively correlated with the variation in disease activity, number of swollen and tender joints, and RF and CRP levels [47]. Onishi et al. reported a significant decrease in ACPA levels on time, only in the group of responder patients, during etanercept treatment [43].

Bobbio-Pallavicini et al. reported that ACPA titers do not decrease during adalimumab treatment [41]. Atzeni et al. reported that adalimumab treatment induced a significant decrease in ACPA serum levels, and the decreased antibody titers correlated with the clinical response to therapy [48]. Bos et al. reported a significant decline in ACPA levels mainly in the responder group of patients to adalimumab treatment [49]. Our group studied the evolution of ACPA titers during a period of time in a group of patients treated with adalimumab. A progressive decrease in ACPA levels was observed throughout the course of adalimumab treatment, but only in the responder group of patients [45].

There is great discrepancy among these studies. Some do not report a decrease in ACPA levels; however, other studies do demonstrate decreased titers, mainly in responder patients.

The presence of −308 TNF G/G genotype appears to be a marker of good response to anti-TNF treatment when DAS28 index is used. ACPAs have been linked to erosive

disease, and have been established as the single most reliable prognostic factor in clinical practice. To test the hypothesis that the ACPA status may affect the -308 G/G rate of response to TNF blockade on patients, we prospectively investigated a group of 52 RA patients with the −308G/G genotype who were ACPA positive or ACPA negative. All patients were treated with adalimumab, and the clinical response was studied using DAS28 at 24 weeks of treatment. No significant differences were found between patients from both groups, according to the DAS28 criteria of response at week 24. In conclusion, these findings suggest that ACPA status does not affect clinical response to anti-TNF therapy in −308 TNF G/G patients [50].

Summary

The TNF-blocking agents, although very effective treatments for RA, are expensive and elicit a variable response in patients with RA. Studies published so far on the pharmacogenetics of the anti-TNF therapies in RA show conflicting results. While some studies suggest that TNF promoter polymorphisms such as −308 G/A correlate with clinical response to anti-TNF therapies, others contradict this finding. Pharmacogenetic studies of anti-TNF therapies have focused on the TNF locus. Nevertheless, it should be emphasized that none of the variants that have been associated with response to TNF antagonists have yet been validated as clinical markers of response to therapy.

The majority of the studies demonstrate a correlation between the presence of high baseline titers of RF and decreased response to anti-TNF treatment. Also, most studies show decreased RF titers during anti-TNF treatment mainly in patients who responded to treatment, on the other hand, there is no consensus about the usefulness of basal ACPA levels as predictor of clinical response to anti-TNF therapy. There is also great discrepancy among various studies: some do not report a decrease in ACPA titers; however, other studies do demonstrate decreased titers, mainly in responder patients.

Despite some promising markers identified to fulfill this role, currently the predictive value of single markers seems

Table 3 Pharmacogenetic studies on TNF blockers using TNF -308 A/G polymorphism

Authors [reference]	Assesment evaluation criteria	No. of patients	TNF blocker	TNFα −308 genotype	Conclusion
Mugnier 2003	↓DAS28≥1.2	53	INF	G/G GA or A/A	TNFα -308 G/G associated with improved response
Padyukov 2003	↓DAS28≥1.2 or ACR20	123	ETA	G/G GA or A/A	No allele significant on its own but a combination of TNFα −308 G/G and TNFα −1087 was associated with improved response to ETN
Cuchacovich 2004	ACR 20	16	IFN	G/G GA or A/A	No association found
Fonseca 2005	↓DAS28≥1.2	22	INF	G/G GA or G/G	TNFα −308 G/G associated with improved response
Cuchacovich 2006	↓DAS28≥1.2	70	ADA	G/G GA or A/A	TNFα −308 G/G associated with improved response
Seitz 2007	↓DAS28≥1.2	54	ETA (n=12) IFN (n=33) ADA (n=9)	G/G GA or A/A	TNFα −308 G/G associated with improved response
Guis 2007	↓DAS28≥1.2	86	ETA	G/G GA or A/A	TNFα −308 G/G associated with improved response
Marotte 2008	ACR20	198	INF	G/G GA or A/A	No association found
Maxwell 2008	↓DAS28≥1.2	1050	ETA (n=453) INF (n=455) ADA (n=142)	GG G/A or A/A	TNFα −308 A/A associated with poor response to ETA
Pinto 2008	↓DAS28≥1.2	113	IFN	G/G G/A or A/A	No association found
Miceli-Richard 2008	ACR50	388	ADA	G/G G/A or A/A	No association found
Pavy 2010	↓DAS28≥1.2	426	ETA (n=36) IFN (n=231) ADA (n=159)	G/G G/A or A/A	No association found

ACR20, American College of Rheumatology 20 % improvement criteria, *ADA* adalimumab, *DAS28* disease activity score using 28 joint counts, *ETA* etanercept, *INF* infliximab

not strong enough to predict treatment response in an individual RA patient. Therefore, future studies should focus not only the identification of novel biomarkers but also the development of prediction models using the combination of several parameters to improve the performance of a biomarker-guided approach.

Conflict of interest All authors declare no conflict of interest.

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