Biological Drug Treatment of Rheumatoid Arthritis and Spondyloarthritis: Effects on QT Interval and QT Dispersion

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ABSTRACT. ***Objective.*** Tumor necrosis factor-α (TNF-α) antagonists bring about significant improvement in chronic inflammatory diseases such as rheumatoid arthritis (RA) and spondyloarthritis (SpA). There is some evidence that they can also have negative myocardial effects, but to date this issue has not been clarified. We evaluated changes in electrocardiographic measures [QT interval, corrected, dispersion, and dispersion corrected (QT, QTc, QTd, QTdc, respectively)] in patients with RA or SpA treated with anti-TNF agents (infliximab and etanercept), those treated with other biological agents (rituximab), and with methotrexate.

Methods. We studied 38 consecutive patients with RA (21 patients) or SpA (19 patients) being treated with TNF-α antagonists, 8 patients with RA being treated with rituximab, and 13 patients (8 with RA and 5 with SpA) taking methotrexate. Electrocardiographs (ECG) were performed on all participants at baseline and 12 months after initiation of treatment, and the QT, QTc, and QTd were calculated with standard procedures.

Results. After 12 months of treatment, significant increases over baseline values were observed in the mean QT ($p < 0.009$), QTd ($p < 0.0001$), and QTdc ($p < 0.0001$) of the anti-TNF group, but no significant changes were observed in those taking rituximab. QT changes in the anti-TNF group were unrelated to the disease (RA vs SpA) or drug (infliximab vs etanercept), and none were associated with clinical manifestations of cardiac disease.

Conclusion. In patients with RA and SpA, TNF-α antagonists seem to increase the QT and QTd measures. Although these changes were completely asymptomatic, ECG may be indicated in patients being considered for anti-TNF therapy to identify those at risk for cardiac complications. (First Release Nov 1 2011; J Rheumatol 2012;39:41–5; doi:10.3899/jrheum.110158)

Key Indexing Terms:
QT INTERVAL TUMOR NECROSIS FACTOR INHIBITOR
RHEUMATOID ARTHRITIS SPONDYLOARTHRITIS QT DISPERSION

Biological agents directed against tumor necrosis factor-α (TNF-α) such as infliximab and etanercept can lead to significant improvement in patients with chronic inflammatory diseases. This therapeutic approach has been approved in several countries for patients with rheumatoid arthritis (RA) or spondyloarthritis (SpA). TNF-α has also been implicated in the pathogenesis of congestive heart failure (CHF), although its effects on the myocardium have not been well defined[1] and it was hypothesized that anti-TNF might also prove useful in the treatment of this disease. Instead, clinical trial data suggest that anti-TNF therapy can actually worsen CHF[2,3]. A report from the US Food and Drug Administration (FDA) notes that in addition to exacerbating existing disease, these drugs may also trigger new-onset CHF, and their use has even been associated with a case of sudden cardiac death (SCD)[4].

Prolongation of the QT interval, a well known electrocardiographic index of ventricular electrical activity, has also been linked to SCD in a community-based cohort of individuals with no evidence of congenital long-QT syndrome[5,6], and noncardiac medications that lengthen the QT interval have been identified as possible risk factors for SCD[7]. The duration of the QT interval on a standard electrocardiograph (ECG) is characterized by interlead differences, which are referred to collectively as QT interval dispersion (QTd). The QTd provides an overall index of the spatial inhomogeneity characterizing ventricular recovery, and the increase of this variable is closely associated with propensity for ventricular arrhyth-

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mias[8]. The QT and QTd are both useful for assessing the cardiac effects of drugs[9].

Our aim was to evaluate QT interval variations in patients with no known heart disease who were being treated with infliximab or etanercept for RA or SpA. For comparison purposes, we also evaluated a group of patients with RA who were being treated with another biological agent (rituximab), as well as a group of healthy subjects taking no medications.

MATERIALS AND METHODS

The protocol for our retrospective, observational study was approved by the Ethics Commission of the Sapienza University of Rome, and informed consent was obtained from all participants. Three groups were analyzed. The first (the anti-TNF group) included consecutive patients who (1) fulfilled the American College of Rheumatology (ACR) criteria for RA[10] or the European Spondylarthropathy Study Group criteria[11] for SpA; (2) had active disease; and (3) were eligible for anti-TNF treatment with infliximab or etanercept. The second (a control group) consisted of patients with RA who (1) met ACR criteria for RA; (2) had never received anti-TNF therapy; and (3) were candidates for treatment with rituximab. The third group was composed of patients with RA or SpA who had been treated with methotrexate alone but never with infliximab, etanercept, or rituximab. Candidates were excluded if they were taking drugs with known QT-prolonging effects and/or had ischemic heart disease, hypertension, valvulopathy, diabetes, or thyroid disease.

Patients in the anti-TNF group were treated with infliximab (5 mg/kg every 8 weeks) or etanercept (25 mg twice a week). Those in the rituximab group received two 1000-mg rituximab infusions, 1 at baseline and the second 2 weeks later. This cycle was repeated after 6 months. Patients treated with methotrexate took a standard dose (15 mg/week). Physical examinations, serum electrolyte studies, and standard 12-lead ECG were performed in all 3 groups at baseline (T0) and repeated in the 2 patient groups 12 months after the initiation of treatment (T12).

ECG were recorded at a speed of 25 mm/s and an amplitude of 10 mm/mv. Artifact-free segments were used for all measurements. The QT interval was defined as the interval between the beginning of the QRS complex and the end of the T wave. It was measured manually in all 12 leads in 2 consecutive cycles by 2 physicians who were unaware of the participant's group origin or treatment status at the time of QT measurements. When U waves were present, the end of the T wave was defined as the intersection of the isoelectric line and the tangent of the maximal slope on the downward limb of the T wave[12]. The indices analyzed were the QT interval and the QTd (in both cases, with and without correction for heart rate, as described[13]). The QT and the rate-corrected QT (QTc) were expressed as mean values (in ms) derived from 3–5 cardiac cycles. The QTd was calculated as the difference (in ms) between the longest and shortest QT intervals recorded in the 12 leads.

Statistical analysis. All analyses were performed with the Statistical Package for Social Sciences 13.0 (SPSS, Chicago, IL, USA). Means and SD were calculated for normally distributed variables; medians and ranges were used for those with a non-normal distribution. Intergroup differences were assessed with the Wilcoxon matched pairs test and paired t test. Two-tailed p values were found, and those ≤ 0.05 were considered significant.

RESULTS

Four of the 38 patients enrolled in the anti-TNF group were excluded from analysis because they were started on antidepressant therapy with chlorpromazine during the study (n = 2) or because artifacts were present on their followup ECG (n = 2). Data were therefore analyzed for 34 patients in this group (19 with RA, 15 with SpA). Twenty-six of these patients (17 with RA, 9 with SpA) received etanercept, and the other 8 (2 with RA, 6 with SpA) were treated with infliximab. Table 1 shows the baseline characteristics of this group and of the 2 control groups. There were no significant differences among the anti-TNF, rituximab, and methotrexate groups in age or disease duration.

At baseline, the anti-TNF group already displayed a significantly longer mean QTc than the healthy controls (443.5 ± 25.5 ms vs 425.5 ± 19.0 ms; p = 0.008), but there were no other significant intergroup differences in the QT indices. Table 2 shows the ECG indices before and after treatment in the 3 patient groups. At T12, there were significant increases over baseline values in the QT, QTd, and QTdc in the anti-TNF group, while in the group treated with rituximab and methotrexate, none of these measures displayed any significant posttreatment changes. Table 3 shows the results of subgroup analysis of QT indices in the anti-TNF group. Posttreatment increases in the QT were detected exclusively in the subgroup of patients being treated with either of the anti-TNF agents for RA. In contrast, posttreatment changes in the QTd and QTdc were unrelated to the disease being treated or to the drug used.

DISCUSSION

The increased risk of cardiovascular disease (CVD) documented in patients with RA can be attributed to traditional risk factors as well as to specific proinflammatory factors such as TNF, which is also one of the most important cytokines implicated in the progression of CHF[1]. Patients with CHF, especially those with cardiac cachexia, have been found to have higher serum levels of TNF-α than healthy subjects[4]. Some studies have suggested that the myocardium itself is capable of producing TNF-α, but the mechanism underlying TNF-α-induced cardiac injury has not been elucidated[14]. In patients with CHF, this cytokine diminishes myocardial contractility by directly modulating calcium-dependent processes and reducing ß-adrenergic responsiveness[14]. Moreover, in animal studies, overexpression of TNF-α in the myocardium seems to reproduce all the clinical features of CHF, such as

Table 1. Baseline characteristics of the patients.

Treated with anti-TNF, n = 34	
Women/men	21/13
Age, yrs, mean ± SD	48.6 ± 10.3
RA patients, women/men	19 (17/2)
Mean disease duration, yrs (range)	14.5 (7–25)
Spondyloarthritis patients, women/men	15 (4/11)
Mean disease duration, yrs (range)	15 (8–28)
Treated with rituximab, n = 8	
Women/men	7/1
Age, yrs, mean ± SD	53 ± 9.7
Mean disease duration, yrs (range)	13.1 (4–27)
Treated with methotrexate, n = 13	
Women/men	12/1
Age, yrs, mean ± SD	46 ± 10.6
Mean disease duration, yrs (range)	14.6 (8–25)

TNF: tumor necrosis factor; RA: rheumatoid arthritis.

Table 2. QT interval characteristics at baseline (T0) and after 12 months of treatment (T12) in the anti-tumor necrosis factor (TNF), methotrexate (MTX), and rituximab groups. Data are given in milliseconds.

Variable†	Anti-TNF* Group			MTX Group			Rituximab Group		
	T0	T12	p	T0	T12	p	T0	T12	p
QT	400.88 ± 25.74	414.41 ± 27.10	0.009	390.8 ± 29.2	401.1 ± 28.4	NS	416.2 ± 27.1	416.2 ± 31.9	NS
QTc	443.56 ± 25.55	450.85 ± 27.24	NS	435.4 ± 26.0	439.4 ± 20.3	NS	457.4 ± 19.9	447.6 ± 23.6	NS
QTd	27.94 ± 8.8	42.94 ± 10.01	< 0.0001	29.2 ± 9.7	32.3 ± 11.1	NS	31.2 ± 8.8	27.5 ± 9.6	NS
QTdc	31.38 ± 11.33	46.71 ± 11.0	< 0.0001	32.4 ± 10.9	35.1 ± 11.2	NS	34.2 ± 9.2	29.4 ± 10.0	NS

* Etanercept or infliximab. † QT measurements (measured in ms): QTc = rate-corrected QT interval; QTd = QT dispersion; QTdc = rate-corrected QT dispersion. NS: not significant.

Table 3. Subgroup analysis of the QT interval characteristics at baseline (T0) and after 12 months of treatment (T12) in the anti-TNF group. QT measured in ms: QTc = rate-corrected QT interval; QTd = QT dispersion; QTdc = rate-corrected QT dispersion.

Variable†	Rheumatic Disease Being Treated						Anti-TNF Agent Used					
	RA, n = 19			SpA, n = 15			Etanercept, n = 26			Infliximab, n = 8		
	T0	T12	p	T0	T12	p	T0	T12	p	T0	T12	p
QT	402.10 ± 23.47	414.74 ± 31.69	0.03	399.33 ± 29.15	414.0 ± 20.98	NS	400.0 ± 22.98	413.85 ± 28.15	NS	403.75 ± 35.02	416.25 ± 25.03	NS
QTc	450.53 ± 19.12	455.05 ± 29.76	NS	434.73 ± 30.33	445.53 ± 23.58	NS	443.50 ± 25.50	447.04 ± 28.65	NS	443.75 ± 27.51	463.25 ± 18.32	NS
QTd	27.89 ± 7.13	43.16 ± 9.46	< 0.0001	28.0 ± 10.82	42.67 ± 10.0	0.0002	28.85 ± 9.52	43.08 ± 10.11	< 0.0001	25.0 ± 5.34	42.5 ± 10.35	0.0008
QTdc	31.31 ± 7.97	47.0 ± 9.58	< 0.0001	31.47 ± 14.87	46.33 ± 12.94	0.0007	32.42 ± 12.24	46.35 ± 10.51	< 0.0001	28.0 ± 7.29	47.87 ± 13.2	0.002

TNF: tumor necrosis factor; RA: rheumatoid arthritis; SpA: spondyloarthritis. NS: nonsignificant.

cardiac hypertrophy, ventricular dilatation, fibrosis, and several of the biochemical and cellular changes associated with the disease[15].

Although the mechanism by which TNF-α provokes cardiac injury is still unclear, its central role in the pathogenesis of CHF has raised additional interest in the agents capable of blocking its activity. Preliminary short-term studies suggested that TNF-α inhibition with the recombinant chimeric soluble TNF-α receptor etanercept might actually benefit patients with CHF[15]. Later, however, in the multicenter RENAISSANCE and RECOVER trials[3], etanercept displayed no efficacy in patients with New York Heart Association class II–IV heart failure, and both trials were terminated early. Moreover, in the ATTACH trial, the group of patients treated with the chimeric monoclonal anti-TNF-α antibody infliximab presented dose-related increases in mortality and heart failure rates, as compared with those receiving placebo[2].

On the basis of these findings, the FDA has advised caution in prescribing anti-TNF agents for patients with CHF. From the time these drugs were licensed through February 2002, the FDA's MedWatch program received voluntary reports of 38 cases of heart failure and 9 of heart failure exacerbations in patients receiving etanercept or infliximab, in most cases (over 80%) for RA[4]. Interestingly, in half of the described cases of new-onset heart failure, no traditional risk factor for heart failure (previous myocardial infarction, coronary artery disease, hypertension, or diabetes mellitus) could be identified. Ten of the 38 patients with incident CHF were 50 years old or younger, and the median interval between the first anti-TNF dose and diagnosis of heart failure was 3.5 months (range 1 day to 2 years)[4].

These findings have not been confirmed in more recent studies. Wolfe and Michaud[16] found significantly ($p < 0.05$) lower rates of heart failure in anti-TNF-treated patients with RA (3.1%; 180/5832) than in patients with RA who were not receiving these drugs (3.8%; 281/7339), even after adjustment for baseline differences. They concluded that in the absence of pre-existing CVD, the risk of heart failure in patients with RA was low (0.4%; 24/6251), and it was not related to anti-TNF therapy. In 2007, similar conclusions were reached by Carmona, *et al*[17]. In their large registry-based study, they found that CV morbidity and mortality in patients with RA were not increased by treatment with TNF antagonists.

Although the current evidence that anti-TNF agents can provoke or worsen CHF in patients with RA is by no means compelling, a better understanding of the myocardial effects of these drugs would probably be useful[1]. Electrocardiography is one of simplest ways to investigate cardiac function, and in the past several years a new surge of interest has been raised in the QT interval, a simple, reproducible marker of the electrical activity of the cardiac ventricles. QT dispersion, the difference between QT intervals recorded in the 12 leads of an ECG, reflects regional differences in myocardial refractoriness, and it has been proposed as a potential predictor of car-

diac dysrhythmias, which are a frequent complication of CHF[18]. The QTd is not an absolute predictor of risk, but it does seem to be useful for investigating the cardiac effects of drugs[9]. Intramyocardial dispersion of repolarization appears to play an important role in both the electrical stability of the ventricles and the generation of arrhythmias such as *torsade de pointes*[19,20]. Lengthening of the QTc interval reflects prolongation of the action potential, and the interval is used as a surrogate marker for predicting this phenomenon as a serious adverse effect of drugs[21].

We examined patients with RA and SpA who did not have CVD before and after treatment with anti-TNF agents. Their ECG displayed significant posttreatment increases in the QT, QTd, and QTdc, which (1) never exceeded normal limits; (2) were never associated with clinical manifestations of any type of CVD; and (3) were unrelated to the underlying disease (RA vs SpA) or to the specific TNF antagonist used (etanercept or infliximab). Findings in this group contrasted with those observed in the control group composed of anti-TNF-naive patients with RA who were treated with the monoclonal anti-CD20 antibody rituximab, and in patients treated with methotrexate. In these patients, the QT and QTd were unchanged after 12 months of therapy.

CVD is a well recognized extraarticular complication of RA and other inflammatory rheumatic diseases. It is usually due to the premature onset of atherosclerosis, and several studies have revealed excess cardiovascular mortality in patients with these disorders[22]. Studies have found significant increases in the QTd in patients with RA, as compared with controls[23], and also in patients with SpA, during the early clinical phases of the disease[24]. In our study, after 1 year of treatment, QT, QTd, and QTdc values were clearly increased in patients treated with anti-TNF agents, whereas no changes of this type were seen in the group that received rituximab or methotrexate. The pathological increase in QT interval and QTd is strongly related to ventricular arrhythmias and sudden death. The relationship between QT interval and heart failure has not been demonstrated. Nevertheless, since 1994, when Barr, *et al*[25] found a significantly greater QT dispersion in patients with ischemic cardiomyopathy who died unexpectedly, QT dispersion has gained increasing interest as a prognostic tool in patients with CHF. To date, the results of various prognostic studies have been conflicting, but in several studies, QT dispersion is greater in patients with CHF than in normal subjects. So even if the relation between QT and CHF is unclear, longer QT is often triggered by a cardiac dysrhythmia, and assessment of the QTd may be useful in predicting these events. It should be stressed that none of the patients in any group developed signs or symptoms of CVD during the followup.

The main limitations of our study are its retrospective design and the small size of the cohort. Moreover, at baseline our patients did not show serum anti-Ro/SSA antibodies, implicated in QT prolongation, but they were not tested after treatment. The arrhythmogenicity of anti-Ro/SSA antibodies for the fetal heart is well established, while it is still a matter of debate for the adult heart[26]. High concentrations of these antibodies have been implicated in QTc interval prolongation in patients with connective tissue disease[27]. However, to our knowledge this is the first study that documents the development of ECG changes after anti-TNF treatment in patients with no evidence of CVD at baseline. It is important to stress that the posttreatment increases in QT and QTd were statistically significant with respect to baseline pretreatment values, but values observed at 12 months were still within the normal range, and none of the ECG changes were associated with appreciable clinical manifestations of cardiac disease. Nonetheless, their presence does suggest that anti-TNF agents are potentially harmful to the myocardium.

A population-based case-control study was conducted in 2005 in the Netherlands using a longitudinal observational database with complete medical records for over 500,000 persons. It showed that the use of QTc-prolonging drugs for the treatment of noncardiac diseases (e.g., those used for gastrointestinal disorders, antipsychotic agents, or antibiotics) increases the risk of SCD in the general population. Although QTc prolongation is not an unusual finding in patients taking these drugs, potentially fatal arrhythmias and SCD are relatively uncommon[7]. In a prospective, single-blind, placebo-controlled, crossover study in 75 patients with RA/SpA, new-onset ventricular tachyarrhythmias were more frequent (8% vs 2.7% during placebo infusion) and more severe during treatment with intravenous infliximab, and the subgroup with tachyarrhythmias had significantly longer baseline QTc values than the group with no arrhythmias[28]. Like our findings, these observations come from relatively small studies, and they must be interpreted with caution. TNF-α antagonists have been widely and successfully used for over 10 years, and there is no compelling evidence that they are unsafe. The adverse cardiac events putatively attributed to these drugs may indeed be quite rare. However, given their potentially life-threatening nature, we, like other authors[7], consider routine assessment of the QT and QTd to be a reasonable precaution for all patients who are being considered for anti-TNF therapy, even those with no evidence of pre-existing cardiac disease. This relatively simple procedure could help identify individuals who are more likely to experience cardiac complications with this type of therapy.

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