Arrhythmic Risk During Acute Infusion of Infliximab: A Prospective, Single-blind, Placebo-controlled, Crossover Study in Patients with Chronic Arthritis

PIETRO ENEA LAZZERINI, MAURIZIO ACAMPA, MOHAMED HAMMOUD, SILVIA MAFFEI, PIER LEOPOLDO CAPECCHI, ENRICO SELVI, STEFANIA BISOGNO, FRANCESCA GUIDERI, MAURO GALEAZZI, and FRANCO LAGHI PASINI

ABSTRACT. ***Objective.*** Reports suggest that infliximab (IFX) may be associated with life-threatening tachyarrhythmias and bradyarrhythmias. We evaluated the prevalence of cardiac rhythm disorders during acute infusion of IFX in a prospective, single-blind, placebo-controlled crossover study of patients with chronic arthritis. Effects of the drug on measures of arrhythmia risk such as QT interval and heart rate variability (HRV) were evaluated.

Methods. Seventy-five patients with spondyloarthritis (SpA; n = 55) or rheumatoid arthritis (RA) underwent an ambulatory 12-channel electrocardiogram (ECG) recording to monitor cardiac arrhythmias, QT interval, and HRV during the infusion of IFX and saline (placebo).

Results. The occurrence of both tachyarrhythmias and bradyarrhythmias was not statistically different during IFX or placebo infusion. During IFX infusion, new-onset ventricular tachyarrhythmias had an 8% incidence (2.7% with placebo; OR 3.17, 95% CI 0.61–16.26) and were more severe. In these patients, mainly with RA, baseline-corrected QT interval and HRV values were significantly prolonged and depressed, respectively, in comparison with subjects without such arrhythmias. IFX acutely produced a significant shift toward a relative vagal prevalence without affecting QT interval measurements.

Conclusion. New-onset cardiac arrhythmias, particularly ventricular tachyarrhythmias, developed during IFX infusion, but their incidence did not achieve statistical significance. We identified some specific risk factors possibly characteristic of the small subset of patients with a higher risk for ventricular arrhythmias. The acute effects of IFX on autonomic balance may substantiate the role of the complex interaction between autonomic nervous system and inflammation during chronic arthritis. (First Release Aug 15 2008; J Rheumatol 2008;35:1958–65)

Key Indexing Terms:
INFLIXIMAB ARRHYTHMIAS HEART RATE VARIABILITY QT INTERVAL
AUTONOMIC NERVOUS SYSTEM INFLAMMATORY REFLEX

Infliximab (IFX) is a human-murine chimeric monoclonal antibody that specifically and potently binds to and neutralizes soluble tumor necrosis factor-α (TNF-α) and its membrane-bound precursor[1]. It has been shown to be an effective treatment for moderate to severe active and fistulizing Crohn's disease[2] and ulcerative colitis[3] when conventional therapies were inadequate, active rheumatoid arthritis (RA), and spondyloarthritis (SpA) that did not responding adequately to disease-modifying antirheumatic drugs (DMARD)[4,5]. However, IFX is associated with several side effects, including the progression of left-ventricular dysfunction in patients with chronic heart failure[6,7]. Recent reports suggest that IFX may be associated with the onset of potentially life-threatening cardiac rhythm disorders. De'Clari, *et al*[8] described a case of sudden death 18 h after a single infusion of IFX in a 64-year-old patient with RA without chronic heart failure, in which post-mortem examination did not provide evidence of an organic cause of death. Boyer, *et al*[9] reported an episode of hemodynamically unstable ventricular tachycardia in a 50-year-old patient with SpA, 24 h after the ninth infusion of IFX. The occurrence of bradyarrhythmias has also been reported. A 22-year-old man with ulcerative colitis showed symptomatic sinus bradycardia (39 beats/min) requiring repeated atropine injections 1 h after IFX administration[10]. Heart block has been described in 4 patients[11-13], among whom a transient type III atrioventricular block developed 30 min after the end of drug infusion in a patient with fistulizing perianal Crohn's disease[12]. Considered together, these data make conceivable the hypothesis that IFX may exert proarrhythmic activities dependent on an indirect effect of alter-

From the Department of Clinical Medicine and Immunological Sciences, Divisions of Clinical Immunology, Internal Medicine, Rheumatology and Cardiology, University of Siena, Siena, Italy.

P.E. Lazzerini, MD, Division of Clinical Immunology; M. Acampa, MD, PhD, Division of Internal Medicine; M. Hammoud, MD, Division of Rheumatology; S. Maffei, MD, Division of Cardiology; P.L. Capecchi, MD, Associate Professor, Division of Clinical Immunology; E. Selvi, MD, PhD; S. Bisogno, MD, PhD; F. Guideri, MD, Research Fellow; M. Galeazzi, MD, Professor, Division of Rheumatology; F. Laghi Pasini, MD, Professor, Division of Clinical Immunology.

Address reprint requests to Dr. P.E. Lazzerini, Department of Clinical Medicine and Immunological Sciences, Division of Clinical Immunology, University of Siena, Siena, Italy. E-mail: pietroenea@yahoo.it

Accepted for publication May 2, 2008.

ations in cardiac inotropism and/or coronary flow[14], or a direct interference effect of the drug on the myocardial electrophysiology. Accordingly, abnormalities in the QT interval dispersion have been reported[15] in a preliminary study performed on 11 children with inflammatory bowel disease receiving IFX.

On the basis of these considerations and because patients with RA and SpA present an intrinsic higher risk of developing arrhythmias and sudden death with respect to the general population[16-19], we evaluated the incidence of cardiac rhythm disorders during acute infusion of IFX in subjects with chronic inflammatory arthropathy. The effects of the drug on some recognized measures of arrhythmia risk, such as QT interval (and QT dispersion) and heart rate variability (HRV)[20], were also evaluated.

MATERIALS AND METHODS

Study population. We studied 75 consecutive patients (46 men) with SpA (n = 55) or RA (n = 20) meeting the criteria of the European Spondylarthropathy Study Group[21] and the American College of Rheumatology[22]. Patients did not have coronary artery disease (CAD), and had no alterations in cardiac enzymes or serum electrolytes, or electrocardiographic (ECG) and/or echocardiographic abnormalities, such as alterations in global or regional contractility (except one patient with chronic heart failure in New York Heart Association class I-II), or in diameters and thickness of the cardiac chambers and walls, respectively. Demographic data and treatment of patients are given in Table 1. All patients received a loading dose of 3–5 mg/kg IFX intravenously at baseline, and at Weeks 2 and 6, followed by scheduled retreatments 8 weeks apart as a maintenance protocol.

The local ethical committee approved the study, and patients gave oral and written informed consent in accord with the Declaration of Helsinki.

All patients underwent consecutive intravenous administration of 250 ml saline in the absence (placebo) and in the presence of 3–5 mg/kg infliximab over a 2 h period for each infusion in a crossover plan in a diagnosis-driven randomization protocol; as a result, placebo infusion preceded and followed IFX administration in 38 and 37 patients, respectively. In all cases, patients had fasted overnight, and the infusions were preceded by a 15 min rest period in a semisupine position on a comfortable armchair. Patients maintained this position over the 2-h infusion period. The subjects were asked to remain awake and relaxed, but the depth and rate of breathing were not controlled. For all patients, the infusions took place between 8:00 AM and 1:00 PM. The study was performed in a single-blind manner, to rule out any psychological conditioning of the patient.

Ambulatory ECG recordings. All patients underwent a 12-channel ECG recording (Prima-Holter, Cardioline, Remco, Vignate-Milano, Italy). ECG

Table 1. Demographic characteristics and treatment of study subjects.

Patients, n	75
Age, yrs	47.2 ± 11.0
Sex, M/F	46/29
Diagnosis, SpA/RA	55/20
Disease duration, yrs	10.4 ± 8.3
Family history of CVD, n	26
Smokers, n	15 (15.7 ± 8.1 cigarettes/day)
Patients with concomitant diseases, n	26
Arterial hypertension, n	14
Inflammatory bowel disease, n	4
Chronic thyroiditis, n	4
Depression, n	3
Diabetes, n	2
Concomitant therapies	60
Steroids*, mean mg	16 (6.5 mg daily)
Methotrexate, mean mg	16 (8.8 mg weekly)
Leflunomide, mean mg	7 (14.1 mg daily)
NSAID	15
Sulfasalazine, mean mg	2 (2250.0 mg daily)
Cyclosporin A, mg	1 (50 mg daily)
Azathioprine, mg	1 (50 mg daily)
ACE/angiotensin II receptor inhibitors	10
Beta blockers	4
Calcium antagonists	5
Diuretics	4
Aspirin	4
Statins	3
Infliximab dose, mg/kg	4.4 ± 0.9
Infliximab therapy duration, mo	26.3 ± 20.6
C-reactive protein, mg/dl; normal < 0.5	0.48 ± 0.66
Erythrocyte sedimentation rate, mm/h; normal < 25	22.9 ± 17.3
Swollen joint count in 66 joints	5.0 ± 4.1
Erosive disease, n	16 (11 RA, 5 SpA)

Except where indicated otherwise, values are mean ± SD. SpA: spondyloarthritis; RA: rheumatoid arthritis; CVD: cardiovascular disease; NSAID: nonsteroidal antiinflammatory drugs; ACE: angiotensin-converting enzyme.

recording was performed for the 15-min period of rest preceding the infusions (baseline), and subsequently for the entire period of intravenous administrations, i.e., 2 h for placebo and 2 h for IFX. The Holter ECG recording was independently analyzed by 2 operators in blinded conditions. Differences were resolved by consensus.

Cardiac rhythm disorders

Tachyarrhythmias. Subjects with ventricular arrhythmias were categorized according to Lown and Wolf[23]. The groups were defined as follows: class 0, no ventricular ectopic beats (VEB); class 1A, < 30 VEB/h, with not more than 1 VEB/min; class 1B, < 30 VEB/h, with ≥ 2 VEB/min; class 2, ≥ 30 VEB/h; class 3, multiform ventricular extrasystole or bigeminal or trigeminal extrasystole; class 4A, ventricular extrasystoles in couplets; class 4B, ventricular tachycardias (i.e., ≥ 3 consecutive VEB with a heart rate > 100 beats/min); and class 5, ventricular extrasystole of the R-on-T type. Frequent or complex ventricular arrhythmias were defined as Lown class 2–5[24]. On this basis, we considered the infusion (IFX or placebo) to be associated with new-onset frequent or complex ventricular arrhythmias when we observed a shift from class 0–1 to class 2–5 (positive patient). Moreover, in the case of frequent or complex tachyarrhythmias in both infusions, an increase in the Lown class (within 2 to 5) was also considered a criterion of positivity.

Following Lown classification[23], we also defined an arbitrary score (ventricular arrhythmia score) aimed at identifying the ventricular arrhythmic load of every patient, as a further comparison tool between the 2 infusion regimens. The score ranged between 0 and 7 and was defined as follows: 0, Lown class 0; 1, Lown class 1A; 2, Lown class 1B; 3, Lown class 2; 4, Lown class 3; 5, Lown class 4A; 6, Lown class 4B; and 7, Lown class 5[25].

Supraventricular arrhythmias were evaluated assessing the prevalence of isolated supraventricular ectopic beats (SVEB), couplets (2 consecutive SVEB), supraventricular tachycardias (defined as ≥ 3 consecutive SVEB), atrial flutter, and fibrillation during placebo and infliximab infusion.

Bradyarrhythmias. The cutoff value for defining sinus bradycardia was set at 50 beats/min, in terms of average rate throughout the infusion period. The prevalence of conduction disturbances, including first, second, and third-degree atrioventricular (AV) block and sinus pauses > 2 s, was also assessed. Similarly to tachyarrhythmias, we considered the IFX or placebo infusion to be associated with new-onset bradyarrhythmias when we observed the novel appearance of conduction disturbances in a patient or worsening in the degree of a preexisting conduction abnormality (positive patient).

QT monitoring. QT interval was continuously monitored during placebo and IFX infusion. The channel with the best signal-to-noise ratio was selected for automatic QT analysis. Analog ECG signals were digitized with a resolution of 12 bits (Acer Italy SRL, Lainate, Italy). To measure corrected QT intervals (QTc), the onset of the QRS and the end of the T wave were detected using an algorithm including the basic steps of ECG signal preprocessing with a low-pass differentiator, corrected QRS detection and definition, T-wave end-definition, and corrected QT value selection (Prima 3/12 CH, Model SW QT, Cardioline, Remco). The T-wave end-definition is based on the first derivative of the ECG signal. To identify T-wave end, a search window was defined from the QRS position. Finally, QT interval was corrected for the heart rate using Bazett's formula[26]. In every patient, the mean QTc interval during each of the 2 infusions was calculated for each of the 12 leads. The leads with the longest mean QTc were considered. QTc was considered abnormal if > 440 ms. QTc dispersion was defined as the difference between the minimum and maximum mean QTc interval among the 12 ECG leads, and considered abnormal if > 50 ms[27].

Heart rate variability measure. HRV was assessed in 2 ways: time-domain analysis and frequency-domain analysis. The mean R-R interval, standard deviation of all R-R intervals (SDNN), standard deviation of the averages of NN intervals in all 5-min segments of the entire recording (SDANN), the square root of the mean of the sum of the squares of differences between adjacent NN intervals (rMSSD), and the number of pairs of adjacent RR intervals differing by > 50 ms in the entire recording divided by the total number of all R-R intervals (pNN50) were measured in the time-domain analysis. SDNN and SDANN quantify, respectively, the overall HRV and the longterm components of HRV. The pNN50 and rMSSD quantify the short-term components of HRV, measuring predominantly vagal activity[28].

Spectral parameters were obtained by the fast-Fourier transform method. Recordings were taken as the means of 5 different 5-min periods[28] that we performed within the last 30 min of every infusion (when the putative effects of the drug were expected to be maximal). The power in the frequency spectrum between 0.003 and 0.40 Hz was defined as total power (VAR), and expressed in ms^2. This power was divided into 3 components: very low frequency (VLF; 0.003–0.04 Hz), low frequency (LF; 0.04–0.15 Hz), and high frequency (HF; 0.15–0.4 Hz). It is believed that HF is a marker of parasympathetic activity and LF a marker of sympathetic (but also vagal) activity. The LF/HF ratio was calculated, as an expression of the sympathovagal balance. High values of this ratio indicate dominant sympathetic activity, whereas low values express a vagal prevalence[28].

Statistical analysis. Statistical evaluation of differences between findings during IFX compared to placebo infusion was performed using 2-tailed Student's t test for paired data for normally distributed continuous variables, and 2-tailed Wilcoxon matched-pairs test for continuous variables not normally distributed. Statistical evaluation of differences between groups categorized on the basis of the presence or absence of new-onset cardiac arrhythmias (positive vs negative patients) was performed using 2-tailed Student's t test for unpaired data for normally distributed continuous variables and 2-tailed Mann-Whitney test for continuous variables not normally distributed. The 2-sided Fisher's exact test or the 2-tailed McNemar's test (paired measurements) was performed to evaluate categorical variables. In any case, $p < 0.05$ was considered significant (GraphPad-InStat, version 3.06 for Windows 2000, GraphPad, San Diego, CA; Microsoft Corp., Redmond, WA, USA).

RESULTS

Cardiac arrhythmias

Tachyarrhythmias. The incidence of ventricular arrhythmias (≥ 1 VEB) and the mean values of VEB per hour (Table 2) were very similar in the 2 infusion regimens. Also, the frequency of frequent or complex ventricular arrhythmias, although slightly different, did not reach statistical significance (Table 2). However, whereas during placebo we found substantially isolated VEB, IFX infusion was associated with repetitive VEB in 3 subjects (including unsustained ventricular tachycardia; Table 2). Accordingly, when employing the ventricular arrhythmia score, which is a more analytical tool to quantify the ventricular arrhythmic load for each patient, we found a difference that indeed approached significance (Table 2).

New-onset frequent or complex ventricular arrhythmias were recorded in 6 patients during IFX infusion, and also in 2 subjects during placebo administration (8% vs 2.7%; OR 3.17, 95% CI 0.61–16.26), but such differences were not statistically significant (Table 2). However, 4 of the 6 patients presenting arrhythmias during IFX infusions (Table 2) showed no ventricular arrhythmias during placebo infusion (Lown class 0), whereas both patients developing arrhythmias with placebo (both in Lown class 3; Table 2) displayed ventricular arrhythmias also during the matching IFX infusion (one in Lown class 1B and one in class 1A). Accordingly, when considering the increase in the ventricular arrhythmia score in patients with new-onset ventricular arrhythmias in both groups, the variation in the IFX group (from 0.5 ± 0.8 to 4.5 ± 0.8) was statistically different ($p < 0.01$), whereas it was not in

Table 2. Tachyarrhythmias, QT interval, and HRV during placebo and infliximab infusion.

Characteristic	Placebo, n = 75	Infliximab, n = 75	p
Ventricular arrhythmias, n (%)	16 (21.3)	21 (28)	0.13
VEB, n/h	5.6 ±32.9	5.0 ± 26.7	0.63
Lown class 2–5, n (%)	5 (6.7)	9 (12)	0.28
Poli, n (%)	3 (4)	3 (4)	
Big/Tri, n (%)	1 (1.3)	3 (4)	
Couplet, n (%)	1 (1.3)	2 (2.7)	
VT, n (%)	0 (0)	1 (1.3)	
Ventricular arrhythmia score	0.48 ± 1.13	0.75 ± 1.49	0.07
Patients with new-onset ventricular arrhythmias, n (%)	2 (2.7)	6 (8)	0.27
Supraventricular arrhythmias, n (%)	14 (18.7)	16 (21.3)	0.83
SVEB, n/h	8.5 ± 65.7	10.4 ± 72.0	0.33
Isolated SVEB, n (%)	13 (17.3)	15 (20)	
Couplets, n (%)	1 (1.3)	1 (1.3)	
SVT, n (%)	0 (0)	0 (0)	
QTc, msec	409.4 ± 23.1	410.1 ± 22.9	0.53
Patients with prolonged QTc, > 440 ms (%)	9 (12)	9 (12)	0.61
Patients with new-onset prolonged QTc (%)	2 (2.7)	2 (2.7)	NS
Maximum mean QTc, ms	470	462	
Minimum mean QTc, ms	365	366	
Median (50th percentile), ms	409	407	
QTcD, ms	33.3 ± 19.0	32.9 ± 22.5	0.30
Patients with increased QTcD, > 50 ms (%)	8 (10.6)	9 (12)	NS
Patients with new onset-increased QTcD (%)	3 (4)	2 (2.7)	NS
RR, ms	882.8 ± 136.4	875.6 ± 125.1	0.26
Heart rate, beats/min	67.0 ± 10.4	68.6 ± 9.8	0.26
rMSSD, ms	41.5 ± 23.5	42.2 ±26.3	0.37
pNN50, %	13.7 ± 14.2	13.8 ± 15.3	0.97
SDNN, ms	73.4 ± 27.8	74.5 ± 31.0	0.57
SDANN, ms	32.7 ± 14.1	34.9 ± 17.6	0.29
VAR, ms^2	3034.0 ± 2720.0	2711.0 ± 2848.7	0.02
VLF, ms^2	701.3 ± 581.4	587.9 ± 524.7	0.006
LF, ms^2	1058.2 ± 1057.3	922.3 ± 1054.8	0.01
HF, ms^2	982.9 ± 1085.8	972.9 ± 1218.7	0.61
LF/HF	1.21 ± 0.48	1.07 ± 0.44	0.0007

Except where indicated otherwise, values are mean ± SD. NS: not significant; VEB: ventricular ectopic beats; Big/Tri: bigeminal or trigeminal VEB; Poli: multiform VEB; VT: ventricular tachycardia; SVEB: supraventricular ectopic beats; QTc: corrected QT interval; QTcD: QTc dispersion; RR: R-R interval; rMSSD: square root of the mean of the sum of the squares of differences between adjacent NN intervals; pNN50; number of pairs of adjacent R-R intervals differing by more than 50 ms in the entire recording divided by the total number of all R-R intervals; SDNN: standard deviation of all R-R intervals; SDANN: standard deviation of the averages of NN intervals in all 5-minute segments of the entire recording; VAR: total power; VLF: very low frequency; LF: low frequency; HF: high frequency; LF/HF: low frequency/high frequency ratio.

the placebo group (from 1.5 ± 0.7 to 4.0 ± 0; p = nonsignificant. Nonparametric ANOVA, Kruskal-Wallis test: p = 0.0052; post-hoc Dunn's multiple comparison test).

Supraventricular arrhythmia showed a similar incidence during both infusions, with no significant difference in the mean hourly number (Table 2). Eight of 75 patients developed new-onset SVEB during IFX infusion, and 6 during placebo infusion (p = nonsignificant; 2-sided Fisher's exact test). In the large majority of cases, SVEB were isolated and infrequent (Table 2). In one patient they were frequently in couplets; whereas they were very frequent (about 500 SVEB/h) although isolated in another subject. However, in both patients, such peculiar characteristics were detectable in a similar manner during either IFX or placebo administration.

Bradyarrhythmias. Evaluating the 75 patients as a whole, no significant difference in the mean heart rate was detected during the 2 different kinds of infusion (Table 2). Bradyarrhythmias occurred asymptomatically in only 2 patients. In one patient we detected some episodes (6) of very transient sinus node dysfunction (1 beat for each), in both IFX (4 episodes) and placebo (2) infusions. However, the duration of sinus pauses was never > 2 s, because of the onset of a junctional escape beat. In the second patient, a short period (about 15 s) of sudden bradycardia (52 beats/min, in the context of a

sinus rhythm of approximately 90 beats/min) with first-degree AV block occurred during placebo infusion, but only after 20 min after the end of IFX administration. In consideration of the long half-life of the drug, it should more likely be attributed to the previously administered IFX.

QTc and QtcD. No significant modifications in the QTc or QTcD were observed when we compared the 2 infusion regimens (Table 2), with mean values below the upper normal limit of 440 ms.

Heart rate variability. With respect to placebo, IFX infusion was associated with evident changes in the autonomic nervous system function when assessed in the frequency domain. Indeed, the administration of the drug produced a significant reduction in the mean values of VAR, together with a concomitant significant decrease in VLF and LF components (Table 2). By contrast, no significant effect of IFX on the HF component was detected (Table 2). As a result, the LF/HF ratio was significantly reduced during IFX infusion compared to placebo (Table 2), as an expression of a relative vagal shift within the autonomic balance.

Conversely, no significant differences arose between the 2 treatment regimens when HRV was measured in the time domain (Table 2).

Potential risk factors for new-onset ventricular arrhythmias during infliximab infusion. To identify potential risk factors that might predispose to the development of new-onset frequent or complex ventricular arrhythmias during IFX administration we compared demographic data, therapy, laboratory data, baseline QT interval, and HRV measures (measured at baseline before the infusion of any substance) of the 6 patients showing new-onset ventricular arrhythmias in the course of drug infusion (positive patients) with IFX and the negative patients not developing such rhythm disturbances (negative patients, n = 69).

The 2 groups demonstrated significant differences concerning QT interval and HRV measures. Indeed, positive patients displayed a significantly longer QTc and a higher prevalence of QTc prolongation compared to negative patients (Table 3). Moreover, all the HRV measures assessed in the frequency domain, particularly total power and LF and HF components, were significantly lower (over 3-fold for each component) in positive compared to negative subjects (Table 3). In this case, time-domain HRV measures also tended to show similar behavior, with lower mean values of SDNN, SDANN, rMSSD, and pNN50 in patients with arrhythmias. However, only differences in pNN50 values achieved statistical significance (Table 3).

Another potential proarrhythmia risk factor was represented by the diagnosis of RA. Indeed, 4 of the 6 positive patients had RA, notwithstanding the 2.5-fold larger prevalence of patients with SpA in the whole study population (Table 3). In other words, new-onset ventricular arrhythmias developed in 20% of RA patients compared to 3.6% of the subjects with SpA. Interestingly, when we evaluated all the patients under study on the basis of the disease diagnosed, we found significant differences in QT interval and HRV measures. Considered together, RA patients compared to SpA subjects displayed longer mean QTc values, higher prevalences of QTc prolongation, and reduced HRV measures in the frequency domain (data not shown). However, all these differences were quantitatively less marked with respect to differences between positive and negative subjects. This suggests that the higher risk of arrhythmia displayed by RA patients might be because these subjects more frequently had QTc prolongation and depressed HRV measures, which eventually might represent the true risk factors.

DISCUSSION

The main results of our study: (1) during IFX infusion new-onset cardiac arrhythmias were observed, particularly ventricular tachyarrhythmias, although in numbers not significantly different from those for placebo; (2) we identified some specific risk factors that may help identify the small subset of patients with a potentially higher risk of arrhythmias that may be life-threatening; (3) IFX administration was associated with an evident acute effect on the autonomic balance, i.e., a decrease in the sympathetic tone with a shift toward a relative vagal prevalence. The occurrence of such an effect, besides representing a potential pathophysiological basis accounting for the cases of bradyarrhythmias reported in the literature, may also substantiate the role of the complex interactions between autonomic nervous system and inflammation in the course of chronic arthritis.

Prevalence and risk factors for ventricular arrhythmias during IFX infusion. In our population, the incidence of new-onset cardiac rhythm disorders associated with IFX infusion appeared to be rather low. Indeed, we detected no significant bradyarrhythmias, whereas tachyarrhythmias developed as a new event in 8% of the subjects in the course of drug administration. Since new-onset tachyarrhythmias were also observed in 2.7% of the patients receiving placebo, the difference did not reach statistical significance (Table 2). In this case, we cannot rule out the possibility that the number of patients studied, although consistent, lacks adequate statistical power to demonstrate the occurrence of a relatively rare, but potentially life-threatening phenomenon[8,9]. Moreover, those new-onset tachyarrhythmias that developed during IFX were more severe than those recorded during placebo, and the relative increase in the arrhythmic load estimated with the ventricular arrhythmia score was significant only for IFX. Accordingly, the subsequent comparison between patients who developed IFX-associated new-onset tachyarrhythmias and those who did not, aimed at identifying specific potential proarrhythmic risk factors, showed many significant differences between the 2 groups. The baseline QTc was significantly and more frequently prolonged, and HRV measures were significantly lower (Table 3) in patients with arrhythmias than in subjects without arrhythmias. Moreover, in agreement

Table 3. Demographic data, therapy, laboratory results, baseline QT interval, and HRV measures: comparison between patients developing or not developing new-onset complex ventricular arrhythmias during IFX infusion.

Characteristic	Positive Patients, n = 6	Negative patients, n = 69	p
Age, yrs	53.6 ± 12.0	46.7 ± 10.9	0.20
Sex, M/F	3/3	43/26	0.67
Diagnosis, RA/SpA	4/2	16/53	0.04
Disease duration, yrs	14.2 ± 10.1	10.0 ± 8.0	0.27
Family history of CVD, n (%)	1 (16.7)	25 (36.2)	0.65
Concomitant diseases, n (%)	1 (16.7)	25 (36.2)	0.65
Hypercholesterolemia, n (%)	1 (16.7)	5 (7.2)	0.40
Smokers, n (%)	0	15 (21.7)	0.34
Concomitant therapies	6	54	
Steroids*, mean mg	3 (6.9 mg daily)	13 (6.2 mg daily)	0.10
Methotrexate, mean mg	3 (10.0 mg weekly)	13 (8.5 mg weekly)	0.10
Leflunomide, mean mg	1 (20 mg daily)	6 (13.1 mg daily)	0.45
NSAID	3	12	0.09
Sulfasalazine, mean mg	0	2 (2250 mg daily)	
Cyclosporin A, mg	0	1 (50 mg daily)	
Azathioprine, mg	0	1 (50 mg daily)	
ACE/angiotensin II receptor inhibitors	1	9	NS
Beta blockers	0	4	
Calcium antagonists	1	4	0.34
Diuretics	0	4	
Aspirin	1	3	0.28
Statins	1	2	0.22
Infliximab dose, mg/kg	4.8 ± 0.4	4.3 ±0.9	0.34
Infliximab therapy duration, mo	18.0 ± 17.3	27.1 ± 17.6	0.30
C-reactive protein, mg/dl; normal < 0.5	0.67 ± 0.38	0.46 ± 0.68	0.08
ESR, mm/h; normal < 25	25.6 ± 8.8	22.6 ± 17.8	0.34
QTc, ms	432.3 ± 29.2	407.3 ± 21.5	0.01
Patients with QTc > 440 ms, n (%)	3 (50)	6 (9.2)	0.02
QTcD, ms	40.7 ± 34.4	32.6 ± 17.2	0.74
rMSSD, ms	28.7 ±22.1	42.5 ± 23.4	0.07
pNN50, %	4.0 ± 5.7	14.6 ± 14.4	0.04
SDNN, ms	57.0 ± 37.3	75.0 ± 26.6	0.13
SDANN, ms	23.8 ± 15.7	33.7 ± 16.7	0.09
VAR, ms^2	1034.2 ± 677.7	3278.2 ± 2794.6	0.01
VLF, ms^2	249.8 ± 262.3	845.4 ± 648.9	0.04
LF, ms^2	301.5 ± 253.1	1149.9 ± 1088.2	0.01
HF, ms^2	289.0 ± 165.4	1057.5 ± 1114.0	0.01
LF/HF	1.02 ± 0.48	1.24 ± 0.56	0.33

Except where indicated otherwise, values are mean ± SD. NS: not significant; SpA: spondyloarthritis; RA rheumatoid arthritis; CVD: cardiovascular disease; NSAID: nonsteroidal antiinflammatory drugs, ESR: erythrocyte sedimentation rate; QTc: corrected QT interval; QTcD: QTc dispersion; RR: R-R interval; rMSSD: square root of the mean of the sum of the squares of differences between adjacent NN intervals; pNN50; number of pairs of adjacent R-R intervals differing by more than 50 ms in the entire recording divided by the total number of all R-R intervals; SDNN: standard deviation of all R-R intervals; SDANN: standard deviation of the averages of NN intervals in all 5-minute segments of the entire recording; VAR: total power; VLF: very low frequency; LF: low frequency; HF: high frequency; LF/HF: low frequency/high frequency ratio.

with other data[17,18,29], we found that the prevalence of these alterations was higher in subjects with RA than in those with SpA. In our opinion, such evidence represents the most conceivable explanation for the significant preponderance of RA patients among the subjects developing new-onset tachyarrhythmias (Table 3). The pathophysiological plausibility of our results is related to the data that both prolongation of QTc and HRV impairment are risk factors for development of life-threatening arrhythmias and sudden death[20]. Many data intriguingly suggest the presence of a chronic sympathetic activation in patients with RA, putatively representing an adaptive response to diminishing the immunoinflammatory activation characterizing the disease. Such an increased sympathetic discharge, possibly responsible for a diminished autonomic reactivity (ß-adrenoreceptor downregulation, reduced responsiveness of the sinus node, and/or central autonomic

regulatory impairment), may account for the increased risk of sudden death in these patients[30-33]. Accordingly, the presence of cardiovascular dysfunction (CAD) in RA was confirmed by HRV analysis, which showed depressed time-domain measures[18]; conversely, the only HRV study performed in patients with SpA showed no evidence of CAD[34]. Such data, in a way consistent with our results, may be related to the higher chronic inflammatory load characterizing patients with RA in comparison to those with SpA.

On the basis of all these considerations, the global depression in HRV measures in those patients developing new-onset arrhythmias with IFX (4 of the 6 patients had RA) may be the maladaptive consequence of a longstanding sympathetic activation (notably, mean disease duration in such patients was about 14 years), whose proarrhythmic effects (including prolongation of QTc[35]) may predispose to an increased risk of ventricular arrhythmias during IFX infusion. Moreover, depressed HRV variability and QTc prolongation are also common findings in advanced chronic heart failure[36,37], in which IFX treatment was unexpectedly found to increase the risk of death and hospitalization[6]; there is an intriguing hypothesis that the drug may exert such deleterious effects in chronic heart failure at least in part by producing cardiac rhythm disorders.

Effects of IFX on the cardiac autonomic system mirror interference with the inflammatory reflex. The acute IFX-dependent decrease in the sympathetic activity (reduction of LF component) with a shift toward a relative vagal prevalence (reduction of LF/HF ratio; Table 2) represents the other main result of our study. This finding is of interest for several reasons. First, it provides a plausible pathophysiological explanation for the severe bradyarrhythmias reported after IFX administration[10-13]. Occurrence of these cases in young patients and absence of preexisting cardiac disability, and their prompt spontaneous or atropine-induced recovery[10,12], suggest functional interference in the conducting system of the heart. Thus, the IFX-associated relative vagal hypertonia we observed might account for the onset of bradyarrhythmias in predisposed subjects.

The second reason of interest deals with the mechanisms putatively involved in such an effect on the autonomic nervous system. As noted above, autonomic activation seems to represent an adaptive mechanism of control of inflammation and immune activation[38]. Many cytokines, including TNF-α, can signal the brain via circulation or through the afferents of vagus nerve and then activate the central components of the sympathetic system[39]. The result is an increase in sympathetic outflow and catecholamine release, which in turn target $ß_2$-adrenergic receptors expressed in lymphocytes and monocytes, inhibiting cytokine production and immunoinflammatory activation[40]. Such a self-controlling loop is a crucial component of the "inflammatory reflex," in which the parasympathetic nervous system also participates in a synergistic manner[40]. Since the central sympathetic system affects not only the immune system but also all body functions under its control, including the heart, it is conceivable that there is cardiac sympathetic overactivity in chronic inflammatory and immunomediated diseases[18,41]. The acute decrease in the LF component (and LF/HF ratio) of HRV observed during IFX infusion suggests that, by decreasing the circulating levels of TNF-α, the drug may interfere with the afferent arm of the loop, reducing the cytokine-driven central sympathetic activation. In this regard, our study provides further indirect evidence for the existence of the inflammatory reflex and the relevance of its sympathetic component in chronic arthritis.

Some potential limitations of our study may have led to underestimation of the incidence of arrhythmias with use of IFX. In particular, an adequate washout period to eliminate any influence of the drug during placebo was lacking, and the sample size, although consistent, may have been insufficient to detect a significant effect of IFX. However, this was an exploratory study designed to obtain a preliminary overview, without a major influence on the patients' compliance. Moreover, it was a single-center study, and sample size was limited. Our results suggest that further studies on a larger population are required to fully address this topic and to avoid the "carryover effect."

For practical clinical application, our results suggest that a brief ECG recording (5–10 minutes) to obtain a frequency-domain HRV analysis and QTc measurement in eligible patients (particularly those with RA) before the onset of IFX therapy may identify the patient subgroup with a relatively higher risk of developing tachyarrhythmias during infusion of the drug. Since such disturbances are potentially life-threatening, ECG monitoring of patients with depressed HRV and/or QTc prolongation may be useful to detect and treat the occurrence of arrhythmias.

ACKNOWLEDGMENT

We thank Prof. Gabriele Cevenini, Department of Surgery and Bioengineering, University of Siena, for his statistical assistance.

REFERENCES

1. Knight DM, Trinh H, Le J, et al. Construction and initial characterization of a mouse-human chimeric anti-TNF antibody. Mol Immunol 1993;30:1443-53.
2. Hanauer SB, Feagan BG, Lichtenstein GR, et al; ACCENT I Study Group. Maintenance infliximab for Crohn's disease: The ACCENT I randomised trial. Lancet 2002;359:1541-9.
3. Rutgeerts P, Sandborn W, Feagan B, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. N Eng J Med 2005;353:2462-76.
4. Maini R, St. Clair EW, Breedveld F, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet 1999;354:1932-9.
5. Braun J, Brandt J, Listing J, et al. Two-year maintenance of efficacy and safety of infliximab in the treatment of ankylosing spondylitis. Ann Rheum Dis 2005;64:229-34.
6. Chung ES, Packer M, Lo KM, Fasanmade AA, Willerson JT; Anti-TNF Therapy Against Congestive Heart Failure Investigators.

Randomized, double blind, placebo-controlled, pilot trial of infliximab, a chimeric monoclonal antibody to tumor necrosis factor-α, in patients with moderate-to-severe heart failure. Results of the Anti-TNF Therapy Against Congestive Heart Failure (ATTACH) Trial. Circulation 2003;107:3133-40.
7. Sarzi-Puttini P, Atzeni F, Shoenfeld Y, Ferraccioli G. TNF-α, rheumatoid athritis and heart failure: a rheumatological dilemma. Autoimmun Rev 2005;4:153-61.
8. De'Clari F, Salani I, Safwan E, Giannacco A. Sudden death in a patient without heart failure after a single infusion of 200 mg infliximab: does TNF-α have protective effects on failing heart, or does infliximab have direct harmful cardiovascular effects? Circulation 2002;105:E183.
9. Boyer JF, Jamard B, El Mahou S, et al. New-onset acute heart failure and ventricular tachycardia after therapy with a tumor necrosis factor antagonist. Clin Exp Rheumatol 2005;23:274-5.
10. Sood A, Midha V. Symptomatic sinus bradycardia with infliximab. Ind J Gastroenterol 2004;23:118-9.
11. Anand CP, Al-Juburi A, Bhargava S. Heart block occurring during infliximab infusion: A report of two cases. Am J Gastroenterol 2003;98:S144.
12. Sofos S, Savoye G, Ramirez S, Bauer F, Lerebours E. Transient type III atrioventricular block after infliximab infusion in a fistulizing perianal Crohn's disease patient. Am J Gastroenterol 2007;102:217-9.
13. Sote Y, Green S, Maddison P. Complete heart block after infliximab therapy. Rheumatology Oxford 2008;47:227-8.
14. Panteris V, Perdiou A, Tsirimpis V, Karamanolis DG. Acute coronary syndrome after infliximab therapy in a patient with Crohn's disease. World J Gastroenterol 2006;12:6235-8.
15. Barbato M, Curione M, Viola F, et al. Cardiac involvement in children with IBD during infliximab therapy. Inflamm Bowel Dis 2006; 12:828-9.
16. Goldelli O, Dursun E, Komsuoglu B. Dispersion of ventricular repolarization: a new marker of ventricular arrhythmias in patients with rheumatoid arthritis. J Rheumatol 1998;25:447-50.
17. Cindas A, Gokce-Kutsal Y, Tokgozoglu L, Karanfil A. QT dispersion and cardiac involvement in patients with rheumatoid arthritis. Scand J Rheumatol 2002;31:22-6.
18. Everengul H, Dursunoglu D, Cobankara V, et al. Heart rate variability in patients with rheumatoid arthritis. Rheumatol Int 2004;24:198-202.
19. Yildirir A, Aksoyek S, Calguneri M, et al. QT dispersion as a predictor of arrhythmic events in patients with ankylosing spondylitis. Rheumatology Oxford 2000;39:875-9.
20. Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. N Eng J Med 2001;345:1473-82.
21. Dougados M, van der Linden S, Juhlin R, et al. The European Spondylarthritis Study Group preliminary criteria for the classification of spondylarthritis. Arthritis Rheum 1991;34:1218-27.
22. Arnett FC, Edworthy SM, Bloch DA, et al. American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
23. Lown B, Wolf M. Approaches to sudden death from coronary heart disease. Circulation 1971;44:130-42.
24. Engstrom G, Hedblad B, Janzon L, Juul-Moller S. Ventricular arrhythmias during 24-h ambulatory ECG recording: incidence, risk factors and prognosis in men with and without a history of cardiovascular disease. J Intern Med 1999;246:363–72.
25. Lazzerini PE, Capecchi PL, Guideri F, et al. Comparison of frequency of complex ventricular arrhythmias in patients with positive versus negative anti-Ro/SSA and connective tissue disease. Am J Cardiol 2007;100:1029-34.
26. Bazett HC. An analysis of the time relations of electrocardiograms. Heart 1920;7:353–76.
27. Malik M, Batchvarov N. Measurement, interpretation and clinical potential of QT dispersion. J Am Coll Cardiol 2000;36:1749–66.
28. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation, and clinical use. Circulation 1996;93:1043-65.
29. Yildirir A, Aksoyek S, Calguneri M, et al. No evidence of cardiac autonomic involvement in ankylosing spondylitis, as assessed by heart rate variability. Clin Rheumatol 2001;20:185-8.
30. Dekkers JC, Geenen R, Godaert GLR, Bijlsma JWJ, an Doornen LJP. Elevated sympathetic nervous system activity in patients with recently diagnosed rheumatoid arthritis with active disease. Clin Exp Rheumatol 2004;22:63-70.
31. Louthrenoo W, Ruttanaumpawan P, Aramrattana A, Sukitawut W. Cardiovascular autonomic nervous system dysfunction in patients with rheumatoid arthritis and systemic lupus erythematosus. QJM 1999;92:97-102.
32. Kuis W, de Jong-de Vos van Steenwijk CCE, Sinnema G, et al. The autonomic nervous system and the immune system in juvenile rheumatoid arthritis. Brain Behav Immun 1996;10:387-98.
33. Schwemmer S, Beer P, Schölmerich J, Fleck M, Straub RH. Cardiovascular and pupillary autonomic nervous system dysfunction in patients with rheumatoid arthritis — a cross-sectional and longitudinal study. Clin Exp Rheumatol 2006;24:683-9.
34. Yildirir A, Aksoyek S, Calguneri M, et al. No evidence of cardiac autonomic involvement in ankylosing spondylitis, as assessed by heart rate variability. Clin Rheumatol 2001;20:185-8.
35. Zhou S, Cao JM, Tebb ZD, et al. Modulation of QT interval by cardiac sympathetic nerve sprouting and the mechanisms of ventricular arrhythmia in a canine model of sudden cardiac death. J Cardiovasc Electrophysiol 2001;12:1068-73.
36. La Rovere MT, Pinna GD, Maestri R, et al. Short-term heart rate variability strongly predicts sudden cardiac death in chronic heart failure patients. Circulation 2003;107:565-70.
37. Vrtovec B, Delgado R, Zewail A, Thomas CD, Richartz BM, Radovancevic B. Prolonged QTc interval and high B-type natriuretic peptide levels together predict mortality in patients with advanced heart failure. Circulation 2003;107:1764-9.
38. Straub RH. Complexity of the bi-directional neuroimmune junction in the spleen. Trends Pharmacol Sci 2004;25:640-6.
39. Elenkov IJ, Wilder RL, Chrousos GP, Vizi S. The sympathetic nerve — an integrative interface between two supersystems: the brain and the immune system. Pharmacol Rev 2000;52:595-638.
40. Tracey KJ. The inflammatory reflex. Nature 2002;420:853-9.
41. Lazzerini PE, Acampa M, Guideri F, et al. Prolongation of the corrected QT interval in adult patients with anti-Ro/SSA-positive connective tissue diseases. Arthritis Rheum 2004;50:1248-52.