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Evaluation of QTc and Tp-e Changes in Rheumatoid Arthritis and Ankylosing Spondylitis Patients Treated with Biological Drugs

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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), but they may have negative myocardial effects**.** This study aimed to evaluate the changes in QT corrected (QTc) and T-peak to T-end (TpTe) in RA and AS patients treated with biological drugs.

Methods: This cross-sectional study included all eligible patients referred to Imam Khomeini Hospital, Urmia, Iran from March 2021 to February 2022 and were randomly divided into two groups (anti-TNF group treated with methotrexate, rituximab, etanercept, adalimumab, infliximab and control group treated with methotrexate). Electrocardiogram (ECG) was performed on all participants at baseline and 6 months after initiation of treatment, and the QT, QTd, and TpTe were calculated with standard procedures.

Result: Of 128 patients with RA or AS, 64 patients were included in the anti-TNF group and control group, separately. There was predominance of male gender: 69 (53.9%) vs. 59 (46.1%) among all patients with mean age of 47.77 years. After 6 months (T6), the anti-TNF group already displayed a longer mean QT, QTc, and TpTe interval than control group (418.7±15.6. ms vs. 414.0±17.5 ms; p = 0.03; 461.7±25. 0 vs. 448.3±11.2, p=0.2; 71.4±6.7 vs. 70.4±7.4, p=0.6, respectively). Post treatment increases in the QT were detected exclusively in the subgroup of patients being treated with Infliximab, Etanercept, Adalimumab, Rituximab for RA, which all were significant (P= 0.002, 0.001, 0.001, 0.001, respectively). In contrast, post treatment changes in the QTc and TpTe indices were not outstanding and statistically significant.

Conclusion: This study demonstrated that anti-TNF drugs induce a substantial increase in QT and QTc levels, which can cause considerable risks to patients due to their asymptomatic presentation. Unlike anti-TNF drugs, methotrexate does not cause significant changes in these parameters.

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Introduction

Tumor necrosis factor alpha (TNF-α) is a versatile cytokine that exerts diverse effects on numerous cell types [1]. It is widely recognized as a key orchestrator of inflammatory responses and plays a pivotal role in the development of various inflammatory and autoimmune disorders [2]. The

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presence of elevated levels of inflammatory cytokines in patients with congestive heart failure (CHF) was initially documented in 1990 [3]. Therapeutic interventions targeting TNF-α, including infliximab, etanercept, and adalimumab, have demonstrated significant clinical benefits across a spectrum of autoimmune and non-autoimmune diseases [4]. This therapeutic strategy has been approved for the treatment of rheumatoid arthritis (RA) and spondyloarthritis (SpA) in several countries [5].

RA is a prevalent systemic inflammatory disorder affecting around 0.5-1% of the population [6]. Notably, RA patients exhibit a substantially elevated risk of heart failure (HF) compared to individuals without RA, even when accounting for established cardiovascular risk factors and coronary artery disease (CAD) [7]. This finding highlights the profound contribution of RA-specific immune/inflammatory pathways to the increased HF risk [8]. Additionally, AS is a chronic multi-systemic inflammatory rheumatologic condition primarily affecting the axial skeleton [9]. AS patients are susceptible to various cardiovascular manifestations, including aortic insufficiency secondary to aortitis, conduction abnormalities, and left ventricular diastolic dysfunction abnormalities attributable to excessive myocardial fibrosis and arrhythmias [10].

Elevated inflammation and sympathetic activity can lead to ventricular depolarization and repolarization abnormalities in patients with RA and AS [11-12]. Surface electrocardiography (ECG) is commonly employed to assess the electrical stability of the heart muscle [13]. Consequently, ventricular arrhythmias can be identified on surface ECG by utilizing the QT interval and T wave as markers of ventricular repolarization [14]. Recent investigations have demonstrated that the Tp-e interval, defined as the duration between the peak and the termination of the T wave on an ECG, can be employed as an index of the overall (transmural, apico-basal, and global) dispersion of repolarization [15]. However, the Tp-e interval is susceptible to variations in body weight and heart rate [16]. Recently, a novel index, the Tp-e/QT ratio, has been proposed as a more precise measure of ventricular repolarization dispersion compared to QTd, QTc, and Tp-e intervals and is independent of heart rate fluctuations [17].

While ventricular repolarization has been previously assessed using T wave and QT interval measurements in patients with RA and AS [18, 19], the novel repolarization indices Tp-e interval and QTc ratio have not yet been investigated in RA and AS patients. This study aimed to evaluate the changes in QTc and Tp-e in RA and AS patients treated with biological drugs (methotrexate, rituximab, etanercept, adalimumab, infliximab).

Materials and Methods

This cross-sectional study was conducted after approval by the ethics committee of Urmia University of Medical Sciences (Code: IR.UMSU.REC.1399.080) and informed consent was obtained from all participants. In this study, all eligible patients referred to Imam Khomeini Hospital, Urmia, Iran from March 2021 to February 2022 were selected and randomly divided into two groups. The first group (anti-TNF group) comprised consecutive patients who met the American College of Rheumatology (ACR) criteria for RA10 or the European Spondylarthropathy Study Group criteria11 for SpA, exhibited active disease, and were eligible for anti-TNF treatment with methotrexate, rituximab, etanercept, adalimumab, or infliximab. The second group (control group) consisted of patients with RA or SpA who fulfilled the ACR criteria for RA and the Spondylarthropathy Study Group criteria for SpA, had never received anti-TNF therapy, and were candidates for treatment with methotrexate (MTX) monotherapy. Exclusion criteria included the use of drugs known to prolong QT intervals, and/or ischemic heart disease, hypertension, valvulopathy, diabetes, or thyroid disease.

Individuals in the anti-TNF group received methotrexate (15 mg/week), rituximab (25 mg twice weekly), etanercept (25 mg twice weekly), adalimumab (25 mg twice weekly), or infliximab (5 mg/kg every 8 weeks). Those in the MTX group received 25 mg of methotrexate, one dose at baseline and a second dose two weeks later. This cycle was repeated after six months. Physical examinations, serum electrolyte studies, and standard 6-lead ECGs were performed in both groups at baseline (T0) and repeated in both groups six months after the initiation of treatment (T6).

Electrocardiography

The 6-lead ECG was recorded with a paper speed of 50 mm/s and amplitude of 10 mm/mV using a Nihon Kohden electrocardiograph (Tokyo, Japan), while the patient was resting in a supine position. Only artifact-free segments of the ECG were considered for analysis. Resting heart rate was

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measured directly from the ECG. QT and TP-e intervals were measured manually by two cardiologists who were blinded to the patient data. To minimize measurement error, calipers and a magnifying glass were used to precisely determine the QT and TP-e intervals. Subjects with U waves on their ECGs were excluded from the study to ensure consistency in data interpretation. The average of three readings for each lead was calculated. The QT interval was measured from the onset of the QRS complex to the end of the T wave and was corrected for heart rate using the Bazett formula: cQT = QTd (R-R interval).

The QTd was quantified as the difference between the longest and shortest QT intervals among the six ECG leads [20]. The normal limits for QTd are 460 ms for women and 450 ms for men, while the minimum limit is 390 ms for both genders. The tail method was utilized to determine TpTe. This approach entails drawing two perpendicular lines from the peak and offset of the T wave, where it intersects the isoelectric line. The horizontal distance between these lines represents the TpTe interval. For a smooth T wave, the perpendicular line is drawn at its midpoint; for a notched T wave, the midpoint of the notch serves as the reference point. The Tp-e interval was measured from the precordial leads [15]. The Tp-e/QT ratio was then calculated. The interobserver and intraobserver coefficients of variation were 3.2% and 2.7%, respectively. All measurements and calculations were overseen by a cardiologist and modified if required to guarantee the study's validity and reliability. All ECG recordings were performed using a single device, and all patients were positioned supine. To measure the intervals, the patients' ECG tapes were scanned, and the desired interval was precisely measured using MATLAB 2018 mathematical software by a qualified engineer.

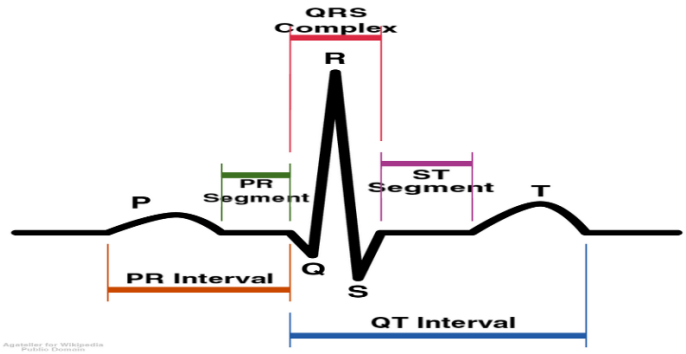

Figure 1: *Illustration of the Electrocardiogram*

Sample sizing

Based on the following formula, and according to the study of DI FRANCO, et al. [21], according to the QT value (intervention group: 2.416 ± 31.9 and control group: 1.400 ± 28.4) and taking into account the confidence interval of 90% and the power of 80%, 64 people were determined in each group.

$$n = \frac{(Z_{1-\alpha/2} + Z_{1-\beta})^2 [P_1(1-P_1) + P_2(1-P_2)]}{(P_1 - P_2)^2}$$

Statistical analysis

All analyses were performed with the Statistical Package for Social Sciences 21 (SPSS, Chicago, IL, USA). The results obtained for qualitative data are reported as percentage and frequency and quantitative data as Mean±SD. T-test was used to compare 2 means and ANOVA test was used to compare more than two means. In case of non-normality of data distribution, non-parametric test equivalents were used. Normality of data distribution was tested using Kolmogorov-Smirnov test. A significance level of less than 0.05 was considered.

Results

Of 128 patients with RA or AS, 64 patients were included in the anti-TNF group and control group, separately. According to Figure 2, there was predominance of male gender: 69 (53.9%) vs. 59 (46.1%) among all patients. In the anti-TNF group, 55.6% (35 people) were men and 44.4% (28 people) were women, and in the control group 51.6% (33 people) were men and 48.4% (31 people) were women. No difference was found respect to gender difference (P=0.65). The mean age of all patients was 47.77 years. In the anti-TNF group it was 48.33 ± 6.65 years old and it was 47.25 ± 8.39 years old in the control group, which was not significant (P=0.42) Figure 3.

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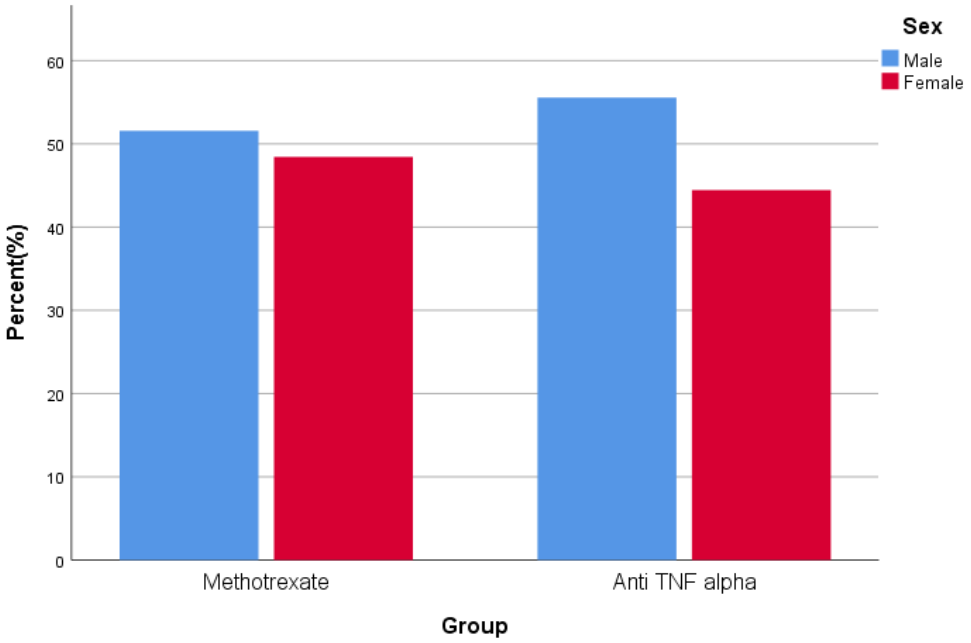

Figure 2: *Sexual distribution of the studied patients in two groups*

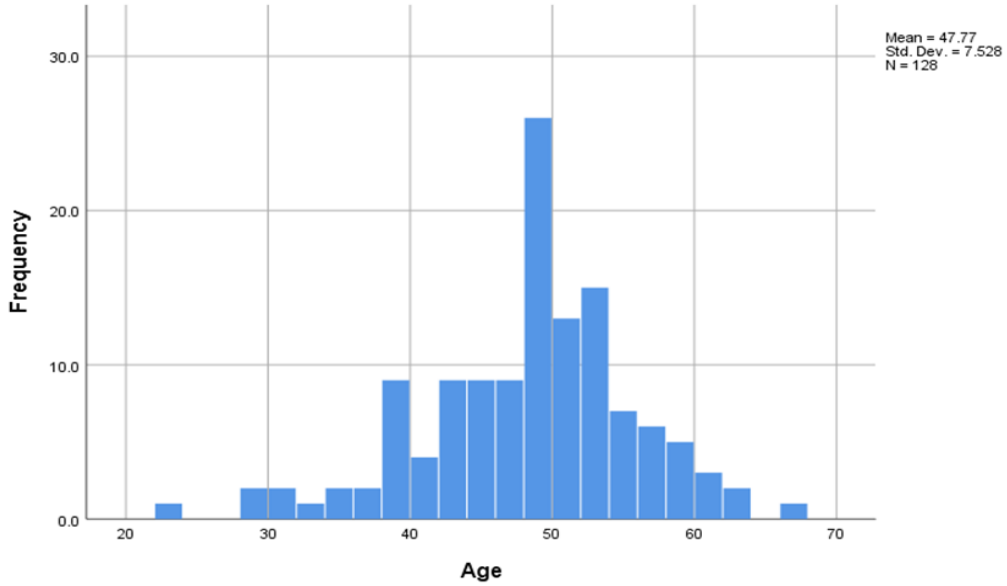

Figure 3: *Age distribution of studied patients*

According to Table 1, at baseline (T0), the anti-TNF group already displayed a significantly shorter mean QT than control group (405.4 ± 10.2 ms vs. 407.1±9.1 ms, p =0.4). Moreover, it longer mean QTc and TpTe than control group (446.5±14.9 vs. 454.6±17.4, p=0.2 and 70.7±7.7 vs. 69.8±8.7, p=0.2, respectively).

After 6 months (T6), the anti-TNF group already displayed a longer mean QT, QTc, and TpTe interval than control group (418.7±15.6. ms vs. 414.0±17.5 ms; p = 0.03; 461.7±25. 0 vs. 448.3±11.2, p=0.2; 71.4±6.7 vs. 70.4±7.4, p=0.6, respectively) (Table 1).

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Table 1: ECG indices at baseline (T0) and after 6 months of treatment (T6) between TNF and control groups. Data are given in milliseconds.

	Anti TNF	Control group		Anti TNF	Control group	
Variables	**T0**		**P-value**	**T6**		**P-value**
QT	405.4±10.2	407.1±9.1	0.4	418.7±15.6	414.0±17.5	0.03
QTc	446.5±14.9	454.6±17.4	0.02	461.7±25.0	448.3±11.2	0.01
TpTe	70.7±7.7	69.8±8.7	0.2	71.4±6.7	70.4±7.4	0.48

Table 2 shows the ECG indices before and after treatment intra groups separately. At T6, there were significant increases over baseline values in the QT, QTC (P<0.001 and P=0.02), But in TpTe examination, although its amount increased after treatment, statistically significant change was not observed (P=0.2). In patients treated with MTX, the mean QT, QTc and TpTe were increased 6 months after the treatment, but no significant difference was observed in any of the investigated criteria before and after treatment (P=0.08, P=0.09 and P = 0.2).

Table 2: *ECG indices at baseline (T0) and after 6 months of treatment (T6) intra group TNF and control groups. Data are given in milliseconds.*

	Anti TNF			Control group		
Variables	**T0**	**T6**	**P-value**	**T0**	**T6**	**P-value**
QT	405.4±10.2	418.7±15.6	<0.001	407.1±9.1	414.0±17.5	0.08
QTc	446.5±14.9	448.3±11.2	0.02	454.6±17.4	461.7±25.0	0.09
TpTe	70.7±7.7	71.4±6.7	0.2	69.8±8.7	70.4±7.4	0.2

Table 3 shows the results of subgroup analysis of QT indices in the anti-TNF group. Post treatment increases in the QT were detected exclusively in the subgroup of patients being treated with Infliximab, Etanercept, Adalimumab, Rituximab for RA, which all were significant (P= 0.002, 0.001, 0.001, 0.001, respectively). In contrast, post treatment changes in the QTc and TpTe indices were not outstanding and statistically significant.

Table 3: *Subgroup analysis of QT indices changes in the anti-TNF group*

Anti-TNF drugs												
	Infliximab			**Etanercept**			**Adalimumab**			**Rituximab**		
	T0	T6	P	T0	T6	P	T0	T6	P	T0	T6	P
QT	404.5±10.7	421.0±15.6	0.002	404.7±10.9	414.25±13.4	0.001	406.9±13.1	420.5±21.8	0.001	405.6±6.2	419.1±10.9	0.001
QTc	447.5±15.7	448.5±12.9	0.3	445.2±10.3	447.5±6.7	0.1	449.6±19.4	449.8±15.9	0.9	444.0±13.8	447.5±7.9	0.08
TpTe	71.2±8.5	71.7±6.3	0.6	66.2±5.8	68.7±6.1	0.1	72.5±6.7	72.8±7.1	0.7	72.7±8.1	72.5±7.0	0.8

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Discussion

Cardiac conduction abnormalities and arrhythmias are significantly more prevalent in RA and AS patients compared to the general population, likely attributed to the increased presence of inflammatory cells, chemokines, and cytokines, myocardial damage, and fibrosis [22]. Individuals with cardiac disorders have been shown to exhibit elevated serum levels of TNF-α compared to healthy counterparts [23]. Moreover, studies have indicated that the myocardium itself can generate TNF-α, but the underlying mechanism of TNF-α-induced cardiac injury remains unclear [24]. Our study investigated the impact of anti-TNF agents on cardiac conduction and arrhythmias in RA and SpA patients without prior CVD. Sure, here is an academically accurate paraphrase of the provided text:

This study demonstrated that patients receiving anti-TNF therapy exhibited significant post-treatment increases in the QT, QTc, and TpTe intervals, but these changes did not exceed normal limits, were not associated with any clinical manifestations of cardiovascular disease (CVD), and were independent of the underlying disease (RA vs SpA) or the specific TNF antagonist used. CVD is a well-established extra-articular complication of RA and other inflammatory rheumatic diseases [25]. It is typically attributed to premature atherosclerosis development, and several studies have revealed elevated cardiovascular mortality in patients with these disorders [26]. Investigations have found notable QTc prolongation in RA patients compared to healthy controls [27], and also in patients with SpA during the early stages of the disease [28].

Our study revealed that after six months of treatment, QT and QTc values significantly increased in patients receiving anti-TNF agents, while TpTe values showed an increment post-treatment but failed to reach statistical significance. No such changes were observed in the MTX group. Pathological prolongation of QT interval and QTc is strongly associated with ventricular arrhythmias and sudden death. DI Franco et al. [21] similarly reported asymptomatically elevated QT intervals and dispersion in patients with inflammatory polyarthritis treated with anti-TNF-α drugs. Abnormalities of ventricular repolarization due to cardiac structural alterations, autonomic dysfunction, and increased inflammatory activity could contribute to increased sudden cardiac deaths and ventricular arrhythmias in RA patients [29]. QTc and TpTe intervals were significantly longer in RA and AS patients compared to the control group, suggesting that increased cardiovascular morbidity and mortality may arise from complex ventricular arrhythmias in these patients [30]. Additionally, Janse van Rensburg et al. [31] reported that impaired autonomic nervous system function could play a crucial role in the development of ventricular arrhythmias in RA and AS.

The Tp-e interval and Tp-e/QT ratio are widely recognized electrocardiographic markers of heightened ventricular repolarization dispersion [32]. These markers are also employed as electrocardiographic indices of ventricular arrhythmogenesis and sudden cardiac death [33]. Prior investigations have demonstrated that prolongation of the Tp-e interval is linked to increased mortality in Brugada syndrome, long QT syndromes, hypertrophic cardiomyopathy, and patients undergoing primary percutaneous coronary intervention for myocardial infarction [34, 35]. Several researchers have examined repolarization patterns in RA patients, observing that QTc is extended compared to controls [29, 36]. However, in these studies, solely QTc was utilized to evaluate the homogeneity of cardiac repolarization, and no information about the association with inflammation was presented. Our study revealed that the Tp-e interval and Tp-e/QT ratio were elevated in RA and AS patients, and these ventricular repolarization indices were correlated with inflammation [37]. Myocardial fibrosis is a recognized complication of RA, thought to arise due to chronic inflammation [38]. Hence, the involvement of myocardial tissue may induce the development of heterogeneity in repolarization, potentially contributing to the emergence of ventricular arrhythmias in RA patients.

Limitations

The primary limitation of our study lies in its cross-sectional design and the absence of patient follow-up. We failed to evaluate the connection between ventricular arrhythmias and Tp-e interval and Tp-e/QT ratio. Additionally, the study population could not be prospectively monitored for ventricular arrhythmic episodes. As a result, we were unable to assess the potential prognostic significance of the electrocardiographic ventricular repolarization indices concerning future adverse events. Long-term follow-up and

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large-scale prospective studies are, therefore, required to determine the predictive value of prolonged Tp-e interval and increased Tp-e/QT ratio in this population. Furthermore, manual measurement of QT and Tp-e intervals on paper-printed electrocardiograms might have weakened the study outcomes as more reliable measurements could be obtained using a high-resolution digital system.

Conclusion

This study demonstrated that Tp-e interval and Tp-e/QT ratio were elevated in RA and AS patients. As previously reported, anti-TNF drugs induce a substantial rise in QT and QTc levels, which can pose considerable risks to patients due to their asymptomatic presentation. In contrast to anti-TNF drugs, our study revealed that MTX does not produce significant alterations in these parameters. Consequently, it can be considered a safer treatment option for RA and AS patients.

Statements and Declarations

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The authors did not receive support from any organization for the submitted work

Competing interests

The authors have no competing interests to declare that are relevant to the content of this article.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Urmia University of Medical sciences (No. IR.UMSU.REC.1399.080).

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Author contributions

M A A: Conceptualization, the original draft writing, investigation, writing including reviewing and editing and investigation and formal analysis; M H P: Conceptualization, supervision, and project administration; T M: Conceptualization, the original draft writing, investigation

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