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Effect of anti-TNFα treatment on Tp-e interval and Tp-e/QT ratio in patients with ankylosing spondylitis: A case-control study

Ankilozan spondilit hastalarında anti-TNFα tedavinin Tp-e mesafesi ve Tp-e/QT oranı üzerine etkisi: Bir vaka-kontrol çalışması

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Abstract

Aim: Ankylosing spondylitis (AS) is an axial spondyloarthropathy with multisystemic involvement. Anti-TNFα agents play a significant role in treatment options of this disease. In the literature, there is contradictory data about the effects of AS disease and anti-TNFα therapy on ventricular repolarization parameters. In this present study, we examined whether electrocardiographic parameters which reflect ventricular repolarization like QT, QTc, Tp-e, Tp-e/QT and Tp-e/QTc are different in AS patients than the control group and the effect of anti-TNFα agents on these parameters.

Methods: Sixty patients diagnosed with AS (33 patients treated with anti-TNFα, 27 patients treated with non-anti-TNFα) and 60 healthy subjects were included in the study. Demographic, biochemical, electrocardiographic, and echocardiographic parameters of the study and control groups were compared. Tp-e interval was measured as the time interval between the T wave's peak point and down slope tangent intersecting with the isoelectric line.

Results: Heart rate, QT, QTc, and QRS were similar in both groups (*P*=0.232, *P*=0.660, *P*=0.220, and *P*=0.846, respectively); Tp-e (*P*=0.013), Tp-e/QT (*P*=0.006), and Tp-e/QTc (*P*=0.041) values were higher in the study group. Comparison analysis performed between groups treated with anti-TNFα and non-anti-TNFα showed no statistically significant difference in terms of heart rate, QT, QTc, QRS, Tp-e, Tpe/QT, and Tp-e/QTc values (*P*=0.916, *P*=0.655, *P*=0.335, *P*=0.999, *P*=0.731, *P*=0.848, and *P*=0.901, respectively).

Conclusion: Although QT and QTc values were similar between AS patients and the control group, Tp-e, Tp-e/QT, and Tp-e/QTc values were higher in AS patients. Additionally, anti-TNFα treatment had a neutral effect on these parameters.

Keywords: Ankylosing spondylitis, T peak-to-end, Tp-e/QT, Anti-TNFα treatment

Öz

Amaç: Ankilozan spondilit (AS) multisistemik tutulumla seyredebilen bir aksiyal spondiloartropatidir. Anti-TNFα ajanlar bu hastalığın tedavisinde önemli bir rol oynarlar. Literatürde AS hastalığı ve anti-TNFα tedavinin ventriküler repolarizasyon parametreleri üzerine etkileri hakkında çelişkili veriler mevcuttur. Sunulan bu çalışmada, QT, QTc, Tp-e, Tp-e/QT ve Tp-e/QTc gibi ventriküler repolarizasyonu gösteren elektrokardiyografik parametrelerin AS hastalarında, kontrol grubuna göre farklı olup olmadığını ve anti-TNFα ajanların bu parametreler üzerinde etkili olup olmadığını araştırdık.

Yöntemler: AS tanılı 60 hasta (anti-TNFα ile tedavi edilen 33 hasta, non-anti-TNFα ile tedai edilen 27 hasta) ve 60 sağlıklı gönüllü çalışmaya dahil edildi. Çalışma ve kontrol grubunun demografik, biyokimyasal, elektrokardiyografik ve ekokardiyografik parametreleri karşılaştırıldı. Tp-e aralığı, T dalgasının tepe noktası ile izoelektrik çizgiyle kesişen aşağı eğim teğeti arasındaki zaman aralığı olarak ölçüldü.

Bulgular: Kalp hızı, QT, QTc ve QRS her iki grupta benzer iken (*P*=0,232, *P*=0,660, *P*=0,220 ve *P*=0,846, sırasıyla); Tp-e (*P*=0,013), Tp-e/QT (*P*=0,006) ve Tp-e/QTc (*P*=0,041) değerleri çalışma grubunda istatistiksel anlamlı olarak daha yüksekti. Anti-TNFα ajanlar ile tedavi edilen ve non-anti-TNFα ajanlar ile tedavi edilen gruplar arasında karşılaştırma analizi yapıldığında ise, kalp hızı, QT, QTc, QRS, Tp-e, Tp-e/QT ve Tp-e/QTc değerlerinde istatistiksel anlamlı farklılık izlenmedi (*P*=0,916, *P*=0,655, *P*=0,335, *P*=0,999, *P*=0,731, *P*=0,848 ve *P*=0,901, sırasıyla).

Sonuç: QT ve QTc değerleri AS hastaları ile kontrol grubu arasında benzer iken; Tp-e, Tp-e/QT ve Tp-e/QTc değerleri çalışma grubunda daha yüksek idi. Ek olarak, anti-TNFα ajanlar bu parametreler üzerine nötral etkiliydi.

Anahtar kelimeler: Ankylosing spondylitis, T peak-to-end, Tp-e/QT, Anti-TNFα treatment

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Introduction

Ankylosing spondylitis (AS) is a chronic and progressive spondyloarthropathy that is more common in young adults. The pathological process of the disease is characterized by bone erosion in sacroiliac joint and vertebral process, new bone formation, and syndesmophyte and ankylosis development in the later stages [1,2]. AS primarily affects the spine, however, it can also be a cause of morbidity and mortality due to multisystemic involvement. These include acute uveitis, peripheral arthritis, enthesitis, psoriasis, aortic root, and gut inflammation [1].

Cardiac involvement is seen in 2-10% of AS patients, being more common in long-term patients [3,4]. The most frequent presentations in cardiac involvement include aortic regurgitation, aortitis at ascending aorta level, rarely mitral insufficiency and conduction system disorders such as atrioventricular block and bundle branch blocks. Additionally, ventricular repolarization abnormalities have also been shown in studies with AS patients. However, no consistent results were obtained on the effects of AS on electrocardiographic parameters that show ventricular repolarization like QT, QTc, QT dispersion, Tp-e and Tp-e/QT [5-7].

Tumor necrosis factor alpha (TNF-α) is an inflammatory cytokine that is contributory in the pathogenesis of AS. Anti-TNFα agents like etanercept, adalimumab and infliximab are options in AS treatment [8]. Previous studies investigated the effects of these agents on ventricular repolarization parameters like QT and QTc and contradictory results were obtained [5,9]. Longo et al. [5] showed that anti-TNFα drugs have neutral effect on QT and QTc intervals; Senel et al. [9] reported shortened QTc interval after infliximab treatment.

In this study, we investigated if ventricular repolarization parameters such as QT, QTc, Tp-e, Tp-e/QT and Tp-e/QTc were higher in AS patients in comparison to the control group and the effect of anti-TNFα drugs on these parameters.

Materials and methods

Study population

In the outpatient clinic of department of physical therapy and rehabilitation of our hospital, patients followed-up with AS diagnosis were reached through hospital database and 60 patients were included in the study. 'ASAS/EULAR recommendations for the management of axial spondyloarthritis' guideline was used for AS diagnosis [10]. Patients were assigned into anti-TNFα treated (n=33) and non-anti-TNFα treated groups (n=27). Sixty age- and gender-matching healthy subjects were included in the study as the control group.

Exclusion criteria included patients with coronary artery disease (CAD), diabetes mellitus (DM), hypertension (HT), moderate-severe valvular heart disease, morbid obesity, liver and kidney dysfunction, active infection, antiarrhytmic medication and the presence of bundle branch block or atrioventricular block.

Disease activity was evaluated by using Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [This index is calculated with parameters like fatigue, spinal pain, peripheral arthritis, enthesitis and morning stiffness severity and duration and 4 or higher scores can indicate active disease.] [11].

Blood samples were obtained on admission from each patient for the measurement of complete blood count, liver and kidney function tests and bleeding profile. 12-hour fasting serum lipid profiles were measured by standard enzymatic methods. Transthoracic echocardiographic (Vivid 7 Dimension, GE Medical Systems, Horten, Norway) examination was performed for each participant.

The study was approved by local ethics committee (Ahi Evran University, number: 2019-14/151 and date: 06/08/2019) and informed consents were obtained from all the participants.

ECG examination

Twelve-lead ECGs were obtained for all participants with a paper speed of 25 mm/s and voltage of 10 mm/mV using a MAC 2000 (GE Medical Systems Information Technologies, Inc., 8200 W, Milwaukee, WI, USA) electrocardiograph while the participant was resting in the supine position. All ECGs were scanned and transferred into digital media and manually evaluated with x400 magnification on a personal computer. ECG measurement values were transferred to the database as the mean value of 3 consecutive beats over precordial lead V5 [12,13].

The QT interval was measured from the beginning of the QRS complex to the end of the T wave and QT interval was corrected using the Bazett's ($QTc=QT/RR^{-2}$) formula [14]. The Tp-e interval was measured by using the tangent method which is calculated as the time interval between the T wave's peak point and down slope tangent intersecting with the isoelectric line [15]. If a U wave followed the T wave, the T wave offset was measured as the nadir between the T and U waves [16]. When the T wave was negative or biphasic, the end point of the T wave was regarded as when the trace returned to the baseline. Then, Tp-e/QT and Tp-e/QTc ratios were calculated.

ECG readings were measured manually by two cardiologists blinded to the participant data. The interobserver and intraobserver coefficients of variation were 3.1% and 2.8%, respectively.

Sample size calculation

Sample size calculation was performed with G-Power 3 calculator at the power of 0.80, alpha error of 0.05 and an estimated effect size of 0.50, which yielded the optimal group size of 60 participants each.

Statistical analysis

SPSS software version 21.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analyses. Normal distribution was assessed with the Kolmogorov-Smirnov and Shapiro-Wilk tests. Descriptive statistics of the variables are represented as mean (standard deviation [SD]) and frequency (n (%)). Independent t test was used for the comparison of two groups. *P*-value of 0.05 was considered statistically significant for all statistical analyses.

Results

Basal demographic, biochemical, electrocardiographic, and echocardiographic characteristics of the study group (n=60) and control group (n=60) are presented in Table 1. In both groups, mean ages (38.91 [9.83] vs 39.80 [12.90], *P*=0.719) and

male gender ratios (75% vs 57%, *P*=0.078) were similar. Thirty-three patients in the study group received anti-TNFα treatments (infliximab: 11, adalimumab: 9, golimumab: 10, and etanercept: 3), while 27 patients were administered NSAIDs.

Table 1: Comparative analysis of demographic, biochemical, and electrocardiographic data of the study and control groups

Variables	Study group (n=60)	Control group (n=60)	*P*-value
Age (years)	38.91 (9.83)	39.80 (12.90)	0.719
Sex (males, %)	45 (75%)	34 (57%)	0.078
BMI (kg/m^2)	25.53 (3.87)	24.37 (2.63)	0.516
Smoking rate (n, %)	34 (57%)	32 (53%)	0.895
Glucose (mg/dL)	90.78 (15.07)	98.76 (12.11)	0.022
eGFR (mL/min)	105.07 (16.73)	99.84 (15.08)	0.179
Total protein (g/dL)	7.26 (0.43)	7.06 (0.40)	0.454
Albumin (g/dL)	4.40 (0.34)	4.90 (0.27)	0.003
Triglyceride (mg/dL)	142.20 (47-391)	137.91 (34-286)	0.828
Total cholesterol (mg/dL)	174.77 (41.06)	175.95 (38.79)	0.912
LDL cholesterol (mg/dL)	101.58 (37.47)	101.58 (36.02)	1.000
HDL cholesterol (mg/dL)	44.00 (12.07)	44.95 (11.72)	0.763
WBC (K/uL)	8.55 (2.06)	7.78 (1.71)	0.094
Platelet (K/uL)	288.55 (62.84)	273.75 (56.17)	0.295
MPV (fL)	10.20 (0.82)	9.98 (0.96)	0.286
hs-CRP (mg/dL)	0.92 (0.02-6.48)	0.24 (0.03-0.78)	0.087
ESR (mm/h)	13.76 (3-67)	-	-
RF (IU/mL)	6.28 (0-25)	-	-
LVEF (%)	63.13 (3.96)	62.75 (2.87)	0.655
BASDAI score	4.22 (0-9.75)	-	-
Electrocardiographic parameters			
Heart rate (beats/min)	77.98 (11.83)	74.86 (10.21)	0.232
QT (ms)	342.57 (23.86)	345.07 (26.03)	0.660
QTc (ms)	389.21 (20.61)	383.13 (22.88)	0.220
QRS (ms)	90.73 (10.86)	91.22 (10.80)	0.846
Tp-e (ms)	68.83 (9.24)	63.80 (7.59)	0.013
Tp-e/QT	0.201 (0.027)	0.185 (0.020)	0.006
Tp-e/QTc	0.177 (0.025)	0.166 (0.016)	0.041
Drug usage for AS			
NSAID (n, %)	27 (45%)	-	-
Infliximab (n, %)	11 (18%)	-	-
Adalimumab (n, %)	9 (15%)	-	-
Golimumab (n, %)	10 (16%)	-	-
Etanercept (n, %)	3 (5%)	-	-

BMI: body mass index, eGFR: estimated glomerular filtration rate, ESR: erythrocyte sedimentation rate, HDL: high density lipoprotein, hs-CRP: high sensitive C-reactive protein, LDL: low density lipoprotein, LVEF: left ventricular ejection fraction, MPV: mean platelet volume, NSAID: nonsteroidal anti-inflammatory drug, RF: rheumatoid factor, WBC: white blood cell

In both groups eGFR, total protein, triglyceride, total cholesterol, LDL cholesterol, HDL cholesterol, WBC, platelet, MPV, and hs-CRP values were similar (*P*=0.179, *P*=0.454, *P*=0.828, *P*=0.912, *P*=1.000, *P*=0.763, *P*=0.094, *P*=0.295, *P*=0.286, and *P*=0.087, respectively). Glucose (90.78 [15.07] vs 98.76 [12.11], *P*=0.022) and albumin values (4.40 [0.34] vs 4.90 [0.27], *P*=0.003) were lower in the study group. Mean values of erythrocyte sedimentation rate (ESR) and rheumatoid factor (RF), which were not evaluated for the control group, were 13.76 and 6.28, respectively, in the study group. Mean BASDAI score in study group was 4.22.

Heart rate, QT, QTc, and QRS were similar in both groups (*P*=0.232, *P*=0.660, *P*=0.220, and *P*=0.846, respectively). Tp-e (68.83 [9.24] vs 63.80 [7.59], *P*=0.013), Tp-e/QT (0.201 [0.027] vs 0.185 [0.020], *P*=0.006) and Tp-e/QTc (0.177 [0.025] vs 0.166 [0.016], *P*=0.041) values were higher in the study group.

When the patients in the study group were divided into two subgroups based on whether anti-TNFα treatment was received, no statistically significant difference was found between the anti-TNFα treatment group (n=33) and the non-anti-TNFα group (n=27) in terms of heart rate, QT, QTc, QRS, Tp-e, Tp-e/QT and Tp-e/QTc parameters (*P*=0.916, *P*=0.655, *P*=0.335, *P*=0.999, *P*=0.731, *P*=0.848, and *P*=0.901, respectively) (Table 2).

Table 2: Comparative analysis of electrocardiographic data from patients with AS treated with anti-TNF-α and non-anti-TNF-α agents

Variables	Treated with anti-TNF-α (n=33)	Treated with non-anti-TNF-α (n=27)	*P*-value
Heart rate (beats/min)	78.13 (11.29)	77.78 (12.74)	0.916
QT (ms)	343.90 (24.51)	340.89 (23.45)	0.655
QTc (ms)	391.68 (18.75)	386.08 (22.77)	0.335
QRS (ms)	90.73 (8.87)	90.73 (13.17)	0.999
Tp-e (ms)	69.23 (7.42)	68.33 (11.28)	0.731
Tp-e/QT	0.202 (0.024)	0.200 (0.031)	0.848
Tp-e/QTc	0.177 (0.019)	0.177 (0.032)	0.901

Discussion

In this study, comparison of AS patients and the control group showed similar heart rate, QRS, QT and QTc values in both groups, whereas, Tp-e, Tp-e/QT and Tp-e/QTc parameters were higher in the study group. In addition, there was no difference in any of the mentioned parameters between the anti-TNFα treatment group and the non-anti-TNFα group among the study group.

Cardiac conduction system disorders and arrhythmias are more common in AS patients compared to the normal population. Atherosclerotic process triggered by the increased amount of inflammatory cells, chemokines, and cytokines, cardiomyocyte damage, and myocardial fibrosis are being suggested as the cause [17,18]. Increased TNFα levels in these patients lead to arrhythmias by causing hypertrophy, apoptosis, fibrosis and consequent dilation in the left ventricle [19]. Conduction system disorders, ranging from bradycardia [5,20] to first [20] and third-degree atrioventricular block [21] are especially caused by interventricular septal fibrosis and atrioventricular nodal anomalies. Also, in patients with AS, supraventricular [22] and ventricular arrhythmias (ventricular extrasystole, couplet, and salvo beats) [23,24] were observed more frequently than in the control group. And recent studies have been focusing on parameters that indicate ventricular repolarization such as QT, QTc, QTd, Tp-e and Tp-e/QT in AS patients. In a study conducted by Yildirir et al. [7] with 88 AS patients, QTd and corrected QTd values were found to be higher in the study group than the control group. And the elevation of these parameters was determined to be associated with the duration of the disease. Longo et al. [5] evaluated 100 patients with spondyloarthropathy, majority of them having AS, and found longer QT interval values in the patient group than the control group and found similar QTc values in both groups. Contradictory to these studies, Kazmierczak et al. [24] found similar QT, QTc and QTd values with the control group in their study where 31 AS patients were evaluated with ECG and 24-hour holter monitoring. In addition to QTd, Acar et al. [6] examined ECG parameters like Tp-e and Tp-e/QT that indicate transmural dispersion of ventricular repolarization [25,26] in AS patients, and found that QTd, corrected QTd, Tp-e and Tp-e/QT parameters were higher in the AS patients in comparison to the control group. In our study, we found similar QT and QTc values in both groups, and higher Tp-e, Tp-e/QT and Tp-e/QTc values in the study group compared against the control group.

Pathophysiology of spondyloarthropathies is still not fully explained. However, inflammatory component of the process is relatively understood with the identification of key immune cell groups and key cytokines like TNFα and interleukin-17 (IL-17). Treatment strategies that target these cytokines are being utilized in a highly effective manner for

disease control. While nonsteroidal anti-inflammatory drug treatment (NSAIDs) can clinically significantly and continuously decrease disease activity [27], by combining anti-TNFα agents with NSAID treatment, additional benefits have been observed in many patients in terms of disease remission [28]. In a recent study, anti-TNFα drugs have been shown to improve cardiovascular functions by decreasing subclinical myocardial inflammation evaluated with cardiac magnetic resonance imaging (CMR) in patients with rheumatoid arthritis, AS and psoriatic arthritis [29]. In addition, the effect of these drugs on ventricular repolarization parameters was also examined in these patients and highly inconsistent results were obtained. In a study by Di Franco et al. [30], anti-TNFa drugs like infliximib and etanercept were shown to increase QT and QTd in comparison to basal value at the end of year 1 in patients with RA and spondyloarthropathy. In another study conducted on spondyloarthropathy patients, no difference was found between QT and QTc values between the groups using and not using anti-TNFa [5]. In a study by Senel et al. [9], intravenous infliximab treatment was administered to 21 AS patients in active period and decrease was observed in QTc compared to basal values at the end of month 6, while there was no difference in terms of QTd values. In our study, previously not studied effects of anti-TNFa drugs on Tp-e, Tp-e/QT and Tp-e/QTc parameters were examined in addition to their effects on QT and QTc intervals and as a result, neutral effects were observed on all of these parameters.

Limitation

The results of the study should be considered and interpreted with several limitations in mind. Firstly, this was a single-center study that had small sample size for the study and control groups. Secondly, the data on the duration of anti-TNFa treatment of the patients was absent. Therefore, regression analysis between the duration of anti-TNFa treatment and electrocardiographic parameters showing ventricular repolarization could not be performed. Due to the small size of the study group, regression analysis was not performed between each anti-TNFa regimen and electrocardiogaphic parameters. Thirdly, measurements were performed manually as the computer software of the ECG device is not available in our facility.

Conclusion

To our knowledge, this study is the first that investigates the effect of anti-TNFα drugs on parameters such as Tp-e, Tp-e/QT and Tp-e/QT that indicate ventricular repolarization in AS patients. Our study revealed higher Tp-e, Tp-e/QT and Tp-e/QT values in the study group than the control group and that anti-TNFα drugs had neutral effect on these parameters. In light of these deductions, evaluation of patients with AS in terms of arrhythmic risk and detection of high-risk patients may help to prevent arrhythmic events. Further, wider-scale studies are needed to validate our results.

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