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Cardiovascular risk assessment after anti-TNF treatment in patients with rheumatoid arthritis and ankylosing spondylitis with Strain Echocardiography

Romatoid artrit ve ankilozan spondilit hastalarında anti-TNF tedavisi sonrası Strain Ekokardiyografi ile kardiyovasküler risk değerlendirmesi

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Abstract

Objective: The aim of this study was to investigate the effects of anti-tumor necrosis factor (anti-TNF) agents on myocardial function and cardiovascular risk factors in rheumatoid arthritis (RA) and ankylosing spondylitis (AS) patients receiving anti-TNF agents for inflammatory arthritis for six months by using standard and speckle tracking echocardiography.

Methods: The study was conducted on a group of 30 patients composed of 12 with RA and 18 with AS. Demographic, standard and speckle tracking echocardiographic data, disease activities, laboratory results related to our research were prospectively assessed.

Results: In the study, there was a statistically significant decrease in disease activity score, Bath Ankylosing Spondylitis Disease Activity index, Health Assessment Questionnaire, and Bath Ankylosing Spondylitis Functional Index scores and erythrocyte sedimentation rate, C-reactive protein values of patients with RA and AS in the sixth month of anti-TNF treatment. There was a decrease in left ventricular global longitudinal strain values assessed with speckle tracking echocardiography in the sixth month compared to the baseline and this difference was statistically significant.

Conclusion: Myocardial strain imaging might be useful in assessing the early development of cardiac failure in patients with high cardiovascular risk, such as patients with RA and AS.

Keywords: Tumor necrosis factor antagonist, cardiovascular risk, rheumatoid arthritis, ankylosing spondylitis

Öz

Amaç: Çalışmanın amacı, romatoid artrit (RA) ve ankilozan spondilit (AS) hastalarında, altı ay süreyle anti-tümör nekroz faktörü (anti-TNF) kullanımının miyokard fonksiyonu ve kardiyovasküler risk faktörleri üzerindeki etkilerini standart ve speckle tracking ekokardiyografi kullanarak araştırmaktır.

Yöntem: Çalışmaya 12 RA ve 18 AS olmak üzere toplam 30 hasta dahil edildi. Araştırmamızla ilgili demografik, standart ve speckle tracking ekokardiyografik veriler, hastalık aktiviteleri, laboratuvar sonuçları prospektif olarak değerlendirildi.

Bulgular: Çalışmada anti-TNF tedavisinin altıncı ayında RA ve AS'li hastaların hastalık aktivite skoru, Bath Ankilozan Spondilit Hastalık Aktivite indeksi, Sağlık Değerlendirme Anketi ve Bath Ankilozan Spondilit Fonksiyonel İndeksi skorlarında ve eritrosit sedimentasyon hızında, C-reaktif protein değerlerinde istatistiksel olarak anlamlı düşüş saptandı. Speckle tracking ekokardiyografi ile değerlendirilen sol ventrikül global longitudinal strain değerlerinde başlangıca kıyasla altıncı ayda istatistiksel olarak anlamlı azalma olduğu saptandı.

Sonuç: Miyokardiyal strain görüntülemesi RA ve AS'li hastalar gibi yüksek kardiyovasküler riski olan hastalarda kalp yetmezliğinin erken gelişimini değerlendirmede yararlı olabilir.

Anahtar Kelimeler: Tümör nekroz faktör antagonist, kardiyovasküler risk, romatoid artrit, ankilozan spondilit

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease of the synovial joints and is the most common autoimmune arthritis.[1] Ankylosing spondylitis (AS) is the most common subtype of spondyloarthropathy and is a chronic inflammatory disease associated with human leukocyte antigen-B27. The prevalence of cardiovascular events, including all grades of atherogenesis from endothelial dysfunction, arterial plaque, thickness in the endothelium, and non-fatal myocardial infarction to stroke, is high in patients with RA and AS.[2-4] Increased cardiovascular events in patients with RA and AS cannot be explained by smoking and other classical risk factors of cardiovascular disease (CVD). Inflammation in patients with RA and AS is considered to play a primary role in cardiovascular events. It has been revealed that the increased risk of CVD in patients, particularly myocardial infarction, increases before the diagnosis of the disease, and it is asserted that systemic inflammation causes atherosclerosis before joint damage. The incidence of cardiovascular events increases as the duration of disease extends in RA.[5-9] Aortitis, conduction defects, valve regurgitation, and cardiomyopathy are among the cardiac complications in patients with AS.[10]

Tumor necrosis factor-alpha (TNF-alpha) is the leading cytokine that promotes inflammation in RA and AS. TNF-alpha levels increase in the synovium and synovial fluid of patients with RA.[11] High levels of inflammatory markers, such as TNF-alpha seem to be associated with the high number of diseased arteries and thereby the severity of coronary artery disease.[12] It was observed that laboratory findings of inflammation decreased, local inflammation of sacroiliac and spinal joints monitored on magnetic resonance imaging (MRI) recovered and clinical activity of the disease rapidly decreased in patients with AS receiving infliximab, etanercept, or adalimumab (anti-TNF agents) treatment. Important improvements monitored on MRI are promising suggesting that these agents may change long-term structural and functional outcomes of AS.[13-15] Although it is considered that anti-TNF treatment will decrease CVD in RA and patients with AS compared to standard treatment, the results in studies differ.[16-19]

Myocardial strain imaging is an advanced echocardiographic method for measuring myocardial deformation during contraction and relaxation.[20] Strain abnormalities have largely been defined for the diagnosis of CVD and are sensitive for the detection of systolic dysfunction in specific diseases causing clinical heart failure with preserved ejection fraction (EF).[21,22] Therefore, an abnormal ventricular strain can be used as a marker of early and subclinical heart failure. In comparison to the controls, significantly lower strain values were observed in patients with RA without CVD.[23]

The reason why patients with RA and AS were included in the study was that TNF-alpha is a common pathogenic cytokine for both inflammatory arthritis and anti-TNF drugs. This study analyzed the change in cardiovascular risk factors in patients with RA and AS after 6-month anti-TNF treatment and to assess EF, left ventricular end-diastolic diameter (LVEDD), and left ventricular end-systolic diameter (LVESD) with standard echocardiography and left ventricular global longitudinal strain (LVGLS) with strain echocardiography.

Materials and Methods

The Marmara University Non-Invasive Clinical Research Ethics Committee approved our study with protocol no 09.2012.0203 in 20.12.2012. The study group included 30 patients (12 RA, 18 AS) who were examined at the Rheumatology Outpatient Clinic of Marmara University between December 2012 and June 2014. Detailed informed consent was obtained from the patients. Twelve patients with RA met the criteria of the 2010 ACR/EULAR RA classification criteria, 18 patients with AS were selected according to ASAS criteria, and none of the patients used anti-TNF drugs before the study. All patients were assessed at the beginning of the treatment and in the 6th month of anti-TNF (infliximab, adalimumab, etanercept, golimumab) treatment. Patients with cardiac failure, valvular heart disease, coronary artery disease, pulmonary disease, liver disease, and renal disease, and patients using cardiac medications were excluded from the study.

Patients' demographic data, characteristics of disease, symptoms, and duration of disease, extra-articular symptoms, classes of medications [disease modifying anti-rheumatic drugs (DMARD) or anti-TNF] were recorded. Also, comorbidities, cardiovascular risk factors such as diabetes mellitus, hypertension, hyperlipidemia, smoking, obesity, and body mass index were recorded. Patients' arterial blood pressure, electrocardiography (NihonKohden, Cardioflex, Japan-12 derivation ECG machine) findings, high-density lipoprotein (HDL), triglyceride (TG), low-density lipoprotein (LDL), total cholesterol, brain natriuretic peptide, and acute phase reactants [erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)] were measured. Disease activity score (DAS)28 was used for patients with RA and Bath Ankylosing Spondylitis Disease Activity index (BASDAI) was used for patients with AS to determine disease activities. Health Assessment Questionnaire (HAQ) and Bath Ankylosing Spondylitis Functional Index (BASFI) were used to determine the functional disability of RA and AS, respectively.

Standard and Two-dimensional Speckle Tracking Echocardiography

All patients underwent a complete transthoracic echocardiographic examination with a commercially available echocardiography device (Vivid 7, GE Vingmed Ultrasound AS, Horten, Norway) with the help of a single experienced cardiologist, who was not aware of the treatment status of the patient. Intrarater correlation analysis was performed to assess reliability.

Data were collected with a 3.5-MHz transducer at a depth of 16 cm in the parasternal and apical views (standard parasternal short-axis from midventricular level, apical long-axis, two-chamber, and four-chamber images). Standard M-mode, 2D, and color-coded tissue Doppler imaging (TDI) parameters were acquired during a breath-hold, stored in a cine loop format from three consecutive beats, and transferred to a work station for further offline analysis (Echo PAC 6.1; GE Vingmed Ultrasound AS). Gain settings, filters, and pulse repetitive frequency were adapted to optimize color saturation, and a color Doppler frame scanning rate of 100-140 Hz was used for color TDI images and grey scale images at a frame rate of 44-82 frames/s. Conventional echocardiographic parameters were measured according to the recent guidelines of the American Society of Echocardiography.[24]

Apical four-chamber, two-chamber, and long-axis views were used for longitudinal strain analysis. End-systolic regions of interest were traced on the endocardial cavity (minimum cavity area) using a point-and-click approach with special care taken to adjust the tracking of all endocardial segments. Global longitudinal strain (GLS) was derived from the average of longitudinal strain values in the apical four-chamber, two-chamber, and long-axis views.

Statistical Analysis

NCSS (Number Cruncher Statistical System) 2007&PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA) was used in statistical analysis. Variables were expressed as numbers and percentiles while descriptive statistics were used for numerical variables (mean, standard deviation, median, minimum, maximum). Fisher's Exact test was used to compare qualitative data, Paired Samples t-test was used for intra-group comparisons of normally distributed parameters, Wilcoxon Signed-Ranks test was used for intra-group comparisons of non-normally distributed parameters and reliability between GLS-1, GLS-2 was assessed by Cronbach's alpha. P<0.05 was considered as a significant value.

Results

Patients' demographic characteristics, smoking history, treatments, and extra-articular involvement are given in Table 1 and Table 2.

Of the patients, 63.3% (n=19) used methotrexate, 80.0% (n=24) used one of the other DMARD and 56.7% (n=17) used steroid.

Comparison of data and laboratory findings after the 6-month treatment is shown in Table 3. Pulse rate, ESR, and CRP significantly decreased after 6 months compared to the beginning.

There was a significant decrease in HAQ, DAS28, BASDAI, and BASFI scores after 6-month anti-TNF treatment (p=0.001, p=0.002, p=0.002, and p=0.028 respectively) (Table 4).

The decrease observed in EF, LVEDD, and LVESD values 6 months after anti-TNF treatment was not

Table 1. Distribution of descriptive characteristics

(n=30)		Median (min-max)
Age		39 (21-62)
Disease duration		2.5 (1-24)
		n (%)
Gender	Male	18 (60)
	Female	12 (40)
Smoking history		14 (46.7)
Smoking (packs/years)		8.5 (1-40)
Active smoking		8 (26.7)
Hypertension		3 (10)
Diabetes mellitus		3 (10)
Hyperlipidemia		1 (3.3)

Non-parametric tests: Median (min-max) values were used. max: Maximum, min: Minimum

Table 2. Disease involvements and treatments

Diagnosis	RA	12 (40)
	Deformity-disability	2 (16.7)
	AS	18 (60)
	Axial involvement	17 (94.4)
	Peripheral arthritis	8 (44.4)
	Enteropathy	1 (5.6)
Extra-articular involvement		2 (6.7)
Uveitis		1 (50)
Keratoconjunctivitis sicca		1 (50)
Anti-TNF	INF	4 (13.3)
	ADA	17 (56.7)
	ETA	6 (20)
	GOLI	3 (10)

ADA: Adalimumab, anti-TNF: Anti-tumor necrosis factor, AS: Ankylosing spondylitis, ETA: Etanercept, GOLI: Golimumab, INF: Infliximab, RA: Rheumatoid arthritis

statistically significant (p>0.01). When we evaluated intra correlation analysis for the GLS-1 and GLS-2 variables in our study, the correlation coefficient was found to be r=0.637, which was statistically moderate reliable. Regarding strain echocardiographic parameters, the decrease observed in LVGLS in the sixth month compared to the pretreatment period was statistically significant (p<0.01) (Table 5).

There was a negative but not statistically significant 31.8% correlation between LVGLS and CRP values at week 0 (r=-0.318; p=0.087; p>0.05) and no statistically significant correlation in terms of changes was observed after 6-month treatment (p>0.05). There was no statistically significant correlation between LVGLS change after 6-month therapy and ESR changes observed in the same period (p>0.05) (Table 6).

Table 3. Comparison of data and laboratory findings at months 0 and 6

	Median, (min-max)		
	Month 0	**Month 6**	**p**
BMI	27.15 (18.00-43.30)	26.35 (18.00-43.30)	0.796
Systolic	120.00 (80-140)	120.00 (80-160)	0.406
Diastolic	80.00 (60-95)	80.00 (60-100)	0.724
Pulse Rate	76.00 (61-96)	70.00 (47-104)	**0.004****
LDL	103.00 (22-158)	102.50 (24-162)	0.489
HDL	45.50 (22-85)	47.50 (28-82)	0.273
TG	97 (43-432)	104.50 (26.00-263.00)	0.261
TG/HDL	2.26 (0.62-16.00)	2.01 (0.64-9.39)	0.199
ESR (n=29)	29 (2-96)	7 (1-48)	**<0.001****
CRP	15.05 (0.10-128.00)	4.15 (0.20-78.90)	**0.021***
ProBNP (n=27)	45 (10-198)	38 (5-197)	0.132

Non-parametric distribution: Wilcoxon Signed Ranks test was used. BMI: Body mass index, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, max: Maximum, min: Minimum, ProBNP: Brain natriuretic peptide, TG: Triglyceride

Table 4. Assessments by HAQ, DAS28, BASDAI, and BASFI

	Month 0	**Month 6**	**p**
	Median (min-max)	**Median (min-max)**	
HAQ (n=30)	0.38 (0.00-2.00)	0.02 (0.00-1.09)	**0.001****
DAS28 (n=12)	4.81 (3.67-7.18)	2.54 (1.12-3.00)	**0.002****
BASDAI (n=18)	5.30 (0.60-8.50)	0.80 (0.00-6.70)	**0.002****
BASFI (n=18)	15.00 (0.00-82.00)	1.00 (0.00-56.00)	**0.028***

*Wilcoxon signed rank test. *p<0.05 **p<0.01. BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, HAQ: Health Assessment Questionnaire, max: Maximum, min: Minimum*

Table 5. Echo and strain values

	Median (min-max)		**p**
n=30	**Month 0**	**Month 6**	
EF	65.00 (51-75)	64.00 (55-75)	0.828
LVEDD	46.50 (37-54)	44.00 (39-57)	0.079
LVESD	29.00 (23-40)	28.00 (23-38)	0.170
LVGLS	21.40 (17.10-28.70)	18.60 (16.40-25.10)	0.001**

*Wilcoxon Signed Ranks test. **p<0.01. EF: Ejection fraction, LVEDD: Left ventricular end-diastolic diameter, LVESD: Left ventricular end-systolic diameter, LVGLS: Left ventricular global longitudinal strain, max: Maximum, min: Minimum*

Table 6. Correlation between LVGLS, CRP and ESR values

LVGLS						
	Month 0		**Month 6**		**Difference**	
	[e]r	**p**	**[e]r**	**p**	**[e]r**	**p**
CRP	-0.318	**0.087**	-0.048	**0.801**	-0.211	**0.263**
ESR	-0.159	**0.401**	0.045	**0.816**	-0.160	**0.408**

[e]r: Spearman correlation coefficient, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, LVGLS: Left ventricular global longitudinal strain

Discussion

In the study, a significant decrease was observed in HAQ, DAS28, BASDAI and BASFI scores, pulse rate, CRP, and ESR after 6-month anti-TNF treatment. LVGLS, one of the strain echocardiographic parameters, was statistically and significantly decreased. No statistically significant change was recorded in EF, LVEDD, and LVESD values, and TG, LDL, HDL, and cholesterol levels.

Although an increased risk of CVD in patients with RA and AS is accepted as multifactorial, an important rate of this increase is considered to be associated with systemic inflammation. An increase in cytokines, such as TNF-alfa causes changes in vascular structures accelerating the atherosclerosis process including endothelial dysfunction, secondary dyslipidemia, and coagulation cascade activation. The early diagnosis of CVD in autoimmune diseases positively affects the long-term prognosis.[25] TNF-alfa inhibition is considered to decrease the development of atherosclerosis and CVD.[16]

Mathieu et al.[26] stated on 34 patients with AS in a 14-week period that increased values of total and HDL cholesterol in patients receiving anti-TNF treatment did not affect the atherogenic index, which is a risk factor for cardiovascular events. There was no change in the TG and LDL-C values of the patients. Spanakis et al.[27] stated on 60 patients (24 with RA, 26 with AS, and 10 with psoriatic arthritis) in 24 weeks that low but continuous increase in serum HDL cholesterol level in patients receiving infliximab treatment for one month may have a positive effect on decreasing the risk of CVD. It was reported in the study by Van Halm et al.[28] that an increase in disease activity in patients with AS was associated with a decrease in lipid levels. The 30 mm increase in ESR in the first hour was associated with a 6% decrease in total cholesterol and an 11% decrease in HDL. The decrease in HDL cholesterol is nearly two times more than the decrease in total cholesterol and causes an atherogenic lipid profile. Kiortsis et al.[29] reported in their study on 82 patients (50 with RA and 32 with AS) in a 6-month period that infliximab treatment had a neutral effect on lipid profile. This was because no significant change was recorded in the total cholesterol/HDL and TG/HDL ratios and in LDL and HDL cholesterol although TG and total cholesterol levels significantly increased. Cauza et al.[30] reported in their study on 15 patients (7 with RA and 8 with Psoriatic arthritis) in the 6 weeks that there was an increase in TG levels of patients after infliximab treatment and a decrease in HDL values. No significant change was recorded in the total and LDL cholesterol levels. Popa et al.[31] recorded an increase in total and HDL cholesterol levels with infliximab treatment in patients with RA in 2 weeks. There were no significant changes in plasma concentrations of lipid fractions excluding TG after 6-month anti-TNF treatment. An increase was recorded in the total cholesterol and LDL-C values after one year of treatment.

Contrary to the study of Mathieu et al.[26], in our study no statistically significant change was recorded in the HDL values of patients after six months anti-TNF treatment, which was similar to the study of Popa et al.[31] In our study, there was no significant difference in TG values, which were different from the findings in the study by Popa et al.[31]. When the lipid levels of the patients were assessed, no statistically significant difference was found in HDL, LDL, TG values in the 6th month of anti-TNF treatment.

There are studies on the standard echocardiography to assess the effect of anti-TNF drugs on cardiac failure. Kotyla et al.[32] reported an increase in the left ventricular EF of patients after a 12-month anti-TNF treatment in their study on 23 patients with RA. In the study by Bragagni et al.[19], a decrease was recorded in the systolic function of 9 patients with RA without cardiac pathology just after infliximab infusion. In the study by Curtis et al.[33], 4,018 patients with RA and Crohn's disease were followed up for 18 months and no significant difference was found between patients receiving TNF-alpha antagonist drugs and those who did not receive, in terms of cardiac failure. Wolfe and Michaud[34] reported in their study on 13,171 patients with RA that cardiac failure was less common in the group anti-TNF treatment group. In the study by Cole et al.[35], there was no significant difference between groups receiving and not receiving anti-TNF treatment in terms of mortality and congestive cardiac failure. In the meta-analysis of Singh, biological agents and other treatment options were compared and no significant difference was found in the incidence rate of congestive cardiac failure.[36] In our study, there was no statistically significant difference between the EF values of patients at the beginning and after 6 months of anti-TNF treatment.

An early assessment of ventricular dysfunction is important in patients with RA especially when starting anti-TNF treatment. Speckle tracking is a non-invasive screening technique for assessing early subclinical dysfunction that cannot be detected by the conventional echocardiography. Although there is no consensus on GLS values in studies on speckle tracking, echocardiography GLS values of patients with RA were lower than those of the healthy control group.

In our study, the clinical activity scores were improved following the biologics, however we noted a deterioration in GLS. In the assessment with standard echocardiography, no statistically significant difference was recorded in EF

and LVEDD six months after the treatment. Sitia et al.[23] compared 20 patients with RA without CVD and 20 healthy controls and found no difference in EF in normal standard echocardiography after 4 months, but there was a significant decrease in left ventricular strain values. Ikonomidis et al.[37] compared 46 patients with RA without CVD and 23 healthy controls and found a significant decrease in strain values in the RA group. In the same study, strain values of patients receiving the interleukin-1 antagonist (anakinra) and 30-day prednisolone treatment were compared and improvement was observed in the left ventricular strain value in the anakinra group. Vizzardi et al.[38] found no change in the GLS value in their study on 13 patients with RA receiving anti-TNF treatment for 1 year. Baniaamam et al.[39] found no changes in GLS and EF values after 6 months of anti-TNF treatment. The reason of the deterioration in GLS in our study may be due to the disease itself or anti-TNF therapy.

Study Limitations

Similar to our study, there were studies in which patients with RA and AS were evaluated together.[27-29] The reason we included two groups in the study were to reach sufficient number of patients. The relatively small study sample may have obscured potentially significant results. The small number of patients (n=30), insufficient follow-up period, the evaluation of patients' echocardiograhic values by a single cardiologist and heterogeneity of the patient group were the limitations of our study.

Conclusion

Assessment with myocardial strain imaging in addition to the standard echocardiography might be a useful method for the follow-up of patients with high cardiovascular risk, such as patients with RA and AS for the early development of cardiac failure.

Ethics

Ethics Committee Approval: This study was approved by the Marmara University Non-Invasive Clinical Research Ethics Committee (approval number: 09.2012.0203, date: 20.12.2012).

Informed Consent: Detailed informed consent was obtained from the patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.P.A., Concept: A.K.Y., N.İ., Design: A.K.Y., A.D., N.İ., Data Collection or Processing: A.K.Y., G.Ö., M.S., Analysis or Interpretation: A.K.Y., A.D., N.İ., Literature Search: A.K.Y., Writing: A.K.Y.

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