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Original article

Anti-TNF-α therapy may not improve arterial stiffness in patients with AS: a 24-week follow-up

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Abstract

Objective. The availability of new-generation drugs has provided significant success reflected by disease activity markers and clinical status in AS, but controversial reports necessitate further assessment of associated increased risk of cardiovascular burden that might persist. Hence this prospective clinical study evaluated the effectiveness of a 24-week anti-TNF-α therapy on vascular stiffness [pulse wave velocity (PWV)] in AS.

Methods. A total of 28 active AS patients (21 males, 7 females) were enrolled before the start of biologic therapy. Demographic and clinical characteristics were recorded. Arterial stiffness was assessed using PWV. Patients were evaluated before and 24 weeks after anti-TNF-α therapy.

Results. The mean disease duration was 8.4 (4.9) years. After 24 weeks of anti-TNF-α therapy, despite significant improvements in patients' symptoms and clinical activity parameters, including BASDAI score [4.9 (0.9) *vs* 1.9 (0.5), $P = 0.0001$], ESR [35.5 (23.1) *vs* 13.8 (9.2) mm/h, $P = 0.0001$) and CRP level [2.1 (1.6) *vs* 0.4 (0.3) ng/dl, $P = 0.0001$], no significant change was seen in arterial stiffness parameters [7.9 (1.3) *vs* 7.7 (1.3) m/s, $P = 0.412$]. Significant correlation was determined between arterial stiffness and age, systolic blood pressure and high-density lipoprotein cholesterol levels.

Conclusion. Despite significant improvement in markers of disease activity, anti-TNF-α therapy does not seem to improve arterial stiffness, a significant AS-associated cardiovascular burden. Thus, when treating AS, significant end-points other than DASs should also be considered, and any hidden threat like arterial stiffness should be addressed further.

Key words: ankylosing spondylitis, anti-TNF-α, pulse wave velocity, arterial stiffness, cardiovascular burden.

CLINICAL SCIENCE

Introduction

AS is a chronic inflammatory rheumatic disease, involving mainly the spine and to a lesser extent peripheral joints, affecting up to 1% of the population [1]. In addition, AS may show extra-articular manifestations including cardiovascular (CV) involvement [1, 2]. The overall mortality of patients with AS is 1.5 times higher than the normal population, and circulatory or CV involvement has been estimated to account for 20–40% [3, 4] of this excess mortality. CV involvement, including aortic involvement causing aortic regurgitation, myocardial involvement associated with conduction defects, arrhythmias and pericardial involvements, in the course of AS are very important extra-articular complications. Although this association has been known for a long time and is common, the exact reasons for this association have not been fully understood. However, inflammation plays a pivotal role in the mechanisms leading to accelerated atherogenesis in patients with AS, and it is likely that chronic systemic inflammation contributes to the increased CV mortality and morbidity [5]. The generalized inflammatory state that characterizes active AS causes these patients to develop CV diseases, as many parallels exist between the inflammatory mechanisms in the pathogenesis of

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atherosclerosis and in the pathogenesis of autoimmune diseases [6]. Indeed, available evidence indicates a significant association between AS and CV burden underlined by the above-mentioned pathophysiological processes, and this aspect of AS-associated long-term morbidity and mortality parameters, considering the subclinical nature of the present atherosclerosis, deserves attention even when disease activity parameters indicate success with applied therapy [2, 5, 7–10].

Subclinical atherosclerosis is considered to be a marker for vascular dysfunction and an independent risk factor for CV disease [11]. Increased TNF-α levels may have an important role in the pathogenesis of endothelial dysfunction in inflammatory diseases [12–14]. Circulating TNF-α levels are increased in patients with AS and are considered important in the pathogenesis of AS [15]. The mechanism of development of subclinical atherosclerosis has been addressed, and endothelial dysfunction is a key early event in atherogenesis, appearing long before the formation of structural atherosclerotic changes [16, 17].

Biological agents, a class of drugs used to achieve therapeutic benefit for inflammatory rheumatic diseases, act by targeting different pathways on immune system mechanisms. TNF-α blocking agents, TNF-α being a key cytokine that plays a role in inflammation, are among the most commonly used members of this class. There is great agreement on the positive effects of anti-TNF-α drugs on disease activity in patients with AS [18]. But information regarding the effects of available therapy, including the biologicals, on AS-associated subclinical atherosclerosis, a well-recognized risk factor for CV burden, is rather scarce and remains uncertain.

With the advances in available therapy choices in AS, despite significant improvement in clinical signs, the consequences of CV structural changes are not known and their establishment may take time. Thus it could be possible that with employment of therapy, satisfactory improvement can be achieved in terms of clinical signs, which may lead to revision of applied therapy, but CV risk could persist and remain. Persistent CV sequelae, including increased arterial stiffness, make patients prone to serious morbidity and mortality risks by causing increased afterload. Thus, when treating patients, it is necessary to focus not only on clinical parameters of patients with AS, but also on the CV disease markers, including the pulse wave velocity (PWV). Hence the aim of this prospective clinical study was to evaluate the effectiveness of a 24-week anti-TNF-α therapy on vascular stiffness (PWV) in relation with clinical signs in patients with AS.

Patients and methods

This study was conducted between September 2009 and September 2010. Twenty-eight AS patients were enrolled. Informed consent was obtained before enrolment, and approval for the study was granted by the local ethical committee of Karadeniz Technical University, Faculty of Medicine, Turkey. The patients with AS met the New York diagnostic criteria [19]. A total of 28 (21 males, 7 females) consecutive patients with AS were scheduled for anti-TNF-α treatment according to the Assessment in AS (ASAS) group guidelines [20]. The patients with AS had long-standing disease duration [mean (S.D.) 8.4 (4.9) years]. Patients did not receive CS treatment during the study. We also excluded patients with diabetes mellitus (fasting blood glucose >7 mmol/l) and patients on anti-hypertensive medications or on lipid-lowering therapies. Patients with a history of CV disease (previous stroke, heart failure, myocardial infarction or angina and peripheral vascular disease) were also excluded.

Clinical assessment

The clinical features of AS patients were recorded. Disease activity was evaluated using the BASDAI (0 = no activity and 10 = highest level of activity). The BASDAI and ESR and CRP levels before and after 24 weeks of treatment were assessed. BMI was calculated as body mass (in kilograms) divided by height (in square metres). Blood pressure was recorded with a mercury column sphygmomanometer. Patients in this study were assessed by a single physician (E.Ç.) who shared information about the protocol of the study.

Laboratory and radiographic examinations

All patients, after a night of fasting (8–12 h), had serum glucose, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol (HDL-C), triglycerides, CRP and ESR analysed.

PWV measurement

By measuring flow and pressure-related waveforms and deriving the vascular distensibility, the aortic PWV method allows valid and highly repeatable detection of information on structure and function [21, 22]. Subjects were asked to omit caffeinated beverages and alcohol for at least 12 h before the assessment. All measurements were performed in a quiet, temperature-controlled room. Every patient was rested in the sitting position, then using a mercury manometer, three blood pressure measurements were taken from the right brachial artery. The average blood pressure measurement was used in the calibration of the equipment. The carotid/femoral PWV measurement was performed using a SphygmoCor system (AtCor Medical, Sydney, Australia) that sequentially records the carotid and femoral artery pulse waves with an application tonometer and ECG. After the patients had been rested for 10 min lying flat on their backs, at least 10 consecutive pulse waves were recorded from the carotid and femoral artery accompanied by application tonometer and ECG. The time difference (t) between the start of each carotid and femoral artery wave was calculated. Using a flexible measure, the total distance (D) between the carotid and femoral artery was measured. After exaggerated values had been excluded, a 10-cycle period average was taken. PWV was calculated as D/t (in metres/second). All non-invasive vascular measurements were performed by the same experienced examiner, who was unaware of the clinical characteristics of the subjects to avoid inter-observer variability.

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Statistical analysis

Continuous variables were expressed as the mean (S.D.). Before statistical applications, the normal distribution of values in this study was verified by normality tests such as the Kolmogorov–Smirnov test. Then parametric statistical analysis was performed. Comparison for repeat analysis was performed using the paired *t*-test. Correlation analysis for continuous variables was performed using the Pearson's correlation coefficient when indicated. A $P < 0.05$ was considered statistically significant.

Results

Clinical characteristics of AS patients are given in Table 1. The mean age of the patients with AS were 33.5 (9.5) years. The mean disease duration was 8.4 (4.9) years. HLA-B27 positivity among AS patients was 82%. The anti-TNF-α treatment involved use of the following three drugs: infliximab, 8 patients; etanercept, 13 patients; and adalimumab, 7 patients. The baseline ESR, CRP and BASDAI score values were 35.5 (23.1) mm/h, 2.1 (1.6) mg/dl and 4.9 (0.9), respectively. After 24 weeks of treatment with anti-TNF-α, BASDAI, ESR and CRP values decreased significantly to 1.9 (0.5), 13.8 (9.2) and 0.4 (0.3), respectively ($P = 0.001$ for all, Table 2).

There was no significant difference in PWV between the pre-treatment and post-treatment [7.9 (1.3) *vs* 7.7 (1.3) m/s, $P = 0.412$, Table 2] values. No significant differences were found in PWV values, measured before and after treatment with anti-TNF-α, between cigarette smokers [7.5 (1.1) *vs* 7.1 (1.5) m/s, $P = 0.297$] and non-smokers [8.3 (1.4) *vs* 8.3 (0.9) m/s, $P = 0.924$]. Augmentation index heart rate (AIx HR 75%) values were not changed significantly after the treatment [21.8 (31.6) *vs.* 11.8 (18.4), $P = 0.177$].

No significant correlation was detected between arterial stiffness and disease activity parameters (CRP, ESR and BASDAI). A significant correlation was determined among the PWV and age, systolic blood pressure and HDL-C levels ($P = 0.04$, $r = 0.383$; $P = 0.01$, $r = 0.629$; $P = 0.02$, $r = -0.569$, respectively; Table 3).

Table 1 Characteristics of AS patients

Disease duration, years	8.4 (4.9)
Male/female, *n*	21/7
Age, years	33.5 (9.5)
HLA-B27 positive, *n* (%)	23 (82)
Current smokers, *n* (%)	12 (42)
BMI, kg/m^2	24.2 (3.7)
Systolic BP, mmHg	107 (14)
Diastolic BP, mmHg	66.8 (11.5)
TC, mg/dl	159.6 (31.5)
LDL-C, mg/dl	87.3 (22.1)
HDL-C, mg/dl	40.1 (10.4)
TG, mg/dl	94.8 (35.2)
BASDAI score	4.9 (0.9)
CRP, mg/dl	2.1 (1.6)
ESR, mm/h	35.5 (23.1)

Values are given as the mean (S.D.) unless otherwise indicated. BP: blood pressure; TC: total cholesterol; TG: triglycerides; LDL-C: low-density lipoprotein cholesterol.

Discussion

Results from this study indicate that a 24-week TNF-α blocking therapy did not significantly improve arterial stiffness in AS, and this was despite significant improvement in clinical signs. It is well-established that inflammation has a role in the development of endothelial impairment, and chronic inflammation leads to accelerated atherogenesis, particularly in RA and AS [23, 24]. It has been shown that male AS patients have a higher CV mortality risk than the general population [4].

It is also clear that the prominent systemic inflammation and related inflammation-driven atherogenesis significantly contributes to the high CV disease risk in AS patients. In most of the recent studies, the presence of subclinical atherosclerosis in AS [2, 5, 7–9] is striking. Therefore attention should be paid to the vascular structures when treating AS patients and evaluating the effectiveness of therapy and long-term morbidity.

There are various methods of assessing vascular function. Local measurement of aortic distensibility by ultrasonography and MRI, regional measurement of PWV by tonometer and Doppler probes and the systemic measurement of arterial stiffness by central waveform shape analysis are the main methods for assessing arterial stiffness. To obtain mechanistic information, local arterial stiffness can be measured directly and non-invasively at various sites along the arterial tree. Problems in characterizing arterial stiffness arise from the complexity of the arterial system, because at different points the physical and chemical wall properties may be different. Therefore we used regional and systemic methods. Aortic PWV is considered as gold-standard measurement of arterial stiffness. It has also been used in epidemiological studies demonstrating the predictive value of aortic stiffness for CV events. Additionally, we evaluated central aortic pressure and AIx HR 75% as a composite marker of wave reflections and arterial stiffness in our study [25, 26].

The positive effect of anti-TNF-α treatment on AS pain, functions, inflammation and extra-articular findings has been shown [18, 27]. But the effects of anti-TNF-α treatment on AS-associated vascular changes is poorly studied [2, 8, 28–30] and the results are controversial.

In addition to the disease activity parameters, the effects of anti-TNF-α treatment on vascular function and the development of atherosclerosis and overall CV risk have been investigated in inflammatory diseases including RA [14, 31–35] and AS [2, 8, 26–28]. A number of studies have investigated their effects on adverse vascular events, most of which have found a favourable effect on reducing the development of atherosclerosis and subclinical CV disease in RA [14, 31–34] and AS [8, 30], although there is some disagreement, as others have found no beneficial vasculoprotective effects. However, all of them have shown biological therapy to be effective in

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Table 2 Comparison of clinical characteristics before and after treatment

Characteristic	Before anti-TNF treatment	After 24 weeks of treatment	*P*-value
BASDAI	4.9 (0.9)	1.9 (0.5)	0.001
CRP, mg/dl	2.1 (1.6)	0.4 (0.3)	0.001
ESR, mm/h	35.5 (23.1)	13.8 (9.2)	0.001
BMI, kg/m^2	24.2 (3.7)	24.5 (3.9)	0.442
Systolic BP, mmHg	107 (14)	108 (11.8)	0.297
Diastolic BP, mmHg	66.8 (11.5)	67.4 (9.4)	0.926
Heart rate	74 (11)	71 (9)	0.821
AP	6.6 (8.1)	5.1 (5.5)	0.631
AIx AP	14.1 (14.7)	15.5 (17.7)	0.732
AIx HR 75%	21.8 (31.6)	11.8 (18.4)	0.177
PWV, m/s	7.9 (1.3)	7.7 (1.3)	0.412

Values are given as the mean (S.D.) unless otherwise indicated. BP: blood pressure; AP: aortic augmentation; AIx AP: aortic augmentation index; $P < 0.05$ (significant).

Table 3 Correlation of parameters with vascular stiffness

Characteristic	PWV	
	r	*P*
Age	0.383	0.04
ESR, mm/h	0.11	0.96
CRP, ng/dl	0.03	0.88
BASDAI	0.33	0.86
Systolic BP, mmHg	0.629	0.01
HDL-C, mg/dl	−0.569	0.02

reducing disease activity. As almost all of these studies involved rather small numbers of patients, it is not clear whether the biologicals, which reduce disease activity, have an additional beneficial effect with regard to CV risk.

Interpretation of the results should also consider possible limitations of this study. Although we could not obtain any significant improvement in PWV (vascular stiffness) with a 24-week anti-TNF-α therapy, we could not comment on whether it prevented further progression of vascular stiffness in patients with AS. Due to ethical restrictions, we could not test this by omitting therapy in these patients with such high disease activity.

Another limitation of the study is that we have no complete data for lipid profiles of the patients. Although there are reports of anti-TNF causing an increase in lipids in some patients, a recent study by Mathieu *et al*. [36] clearly shows no significant effect of 14-weeks TNF-α blockade treatment on the lipid profile in AS patients. So it seems unlikely that possible TNF-α blockade treatment-induced increase could partly explain the lack of change in PWV in our patients.

In agreement with previous studies [2, 8, 14], we have demonstrated the efficacy of 24-week anti-TNF agents (infliximab, etanercept and adalimumab) in reducing disease activity, with no changes in PWV. Therefore we conclude that with the advances in available therapy choices in AS, despite significant improvement in clinical signs, the consequences of CV structural changes are not known and they may take time. Among AS-associated morbidity and mortalities, CV burden is significant, and it seems that despite improvement in markers of disease activity, anti-TNF-α therapy does not seem to improve arterial stiffness in AS in our 24-week follow-up study.

Results from this study indicate that when treating AS, significant end-points other than DASs should also be considered and any hidden threat, like arterial stiffness, should be addressed further. But a more definitive conclusion is that further comprehensive studies are needed.

Rheumatology key messages

- Anti-TNF-α agents reduce AS disease activity without associated improvement in arterial stiffness in a 24-week follow-up.
- PWV can effectively detect vascular functions including subclinical atherosclerosis in patients with AS.

Disclosure statement: The authors have declared no conflicts of interest.

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