Remarkable damage along with poor quality of life in Takayasu arteritis: cross-sectional results of a long-term followed-up multicentre cohort

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Received on May 13, 2016; accepted in revised form on July 29, 2016.

Clin Exp Rheumatol 2017; 35 (Suppl. 103): S77-S82.

Key words: vasculitis, Takayasu arteritis, vasculitis damage index, quality of life

Competing interests: none declared.

ABSTRACT

Objective. *We aimed to assess the outcome of a large Takayasu arteritis (TAK) cohort using the vasculitis damage index (VDI) and quality of life (QoL) scale, tools which have been validated for vasculitis.*

Methods. *Disease activity, damage and QoL were cross-sectionally evaluated in 165 TAK patients from 6 centres. SF-36 were applied to 51 age-matched healthy controls (HC). Persistent activity for ≥6 months was considered as treatment resistance (r-TAK). The correlation between VDI, clinical characteristics and mental (MCS)/physical (PCS) component scores of SF-36 were analysed. SF-36 and VDI scores were compared between TAK subgroups and HC.*

Results. *The median age, follow-up time and disease duration were 40 (17–68), 60 (6–384), and 72 (6–396) months, respectively. 35% of them were r-TAK. VDI scores (VDIs) in TAK 4 (1–12) were mainly due to the disease itself [4 (1–10)]. VDIs in r-TAK were significantly higher than nr-TAK [5 (2–12) vs. 3 (2–10), p<0.001)]. In the TAK patients, MCS and PCS were found as 43±10 and 38±11, respectively. A high proportion of poor MCS (70%) and PCS (80%) were demonstrated in TAK. A significantly negative but weak correlation was observed between VDI and MCS (p=0.003, r=-0.23), PCS (p<0.001, r=-0.34). Higher VDIs were detected in patients with PCS <50 [5 (1–12) vs. 2 (1–6) p<0.001)]. SF-36 score was significantly lower in TAK than HC.*

Conclusion. *Disease-related damage mainly caused by peripheral vascular involvement was more predominant than treatment-related damage without reaching the level of severe damage scores, but contributing to poor QoL, in the TAK cohort.*

Introduction

Takayasu arteritis (TAK) is a chronic, inflammatory disease of unknown aetiology that primarily affects large vessels, such as the aorta and its main branches (1, 2). The extend of vascular involvement, relapsing or smoldering disease activity and irreversibl vascular damage at diagnosis in the majority of patients are the main components that might affect long-term prognosis. Recent studies have been focused on the epidemiology and treatment of large-vessel vasculitis, including cases of TAK (3, 4). However, these studies do not address the issue of damage and quality of life in patients with large-vessel vasculitis, in particular in those with TAK. It's been assumed that morbidity in TAK is resulted from disease and treatment related damage. The Vasculitis Damage Index (VDI) is a well-known validated tool for organ damage assessment in sytemic vasculitides (5). VDI contains items evaluating peripheral vascular damage despite a small number of TAK patients were included into the original validation cohort of VDI (5, 6). Short-form 36 as a validated generic tool of Quality of life (QoL) assessment has long been used as patient reported outcome measure in rheumatic diseases (7, 8). Recent studies have suggested that QoL parameters are impaired in small- to medium-vessel systemic vasculitides (9-14) and also in TAK (15-17).

In this study, we aimed to evaluate the outcome of TAK in a regularly followed-up cohort by VDI and SF-36.

Patients and methods

One hundred and sixty-five consecutive patients (146 female) from six university hospitals in Turkey and followed up more than 6 months were

Table I. The demographic and clinical features of TAK patients.

Gender (Female/male)	146/19
Age at diagnosis, mean ± SD, range	32.5 ± 11.7, (11-64)
Age, yrs, median (range)	40 (18-68)
Time to diagnosis, months, median (range)	14 (1-420)
Disease duration, months, median (range)	72 (6-396)
Follow-up time, months, median (range)	60 (6-384)
Type of vascular involvement, n (%)	
Type I	84 (50.9)
Type IIa	5 (3)
Type IIb	6 (3.6)
Type III	2 (1.2)
Type IV	12 (7.3)
Type V	56 (33.9)
Cumulative GC doses, g, median (range)	6.9 (0-45)
Cumulative GC duration, months, median (range)	48 (0-384)
Cumulative CYC doses, g, median (range)	0 (0-31.5)
Cumulative CYC duration, months , median (range)	0 (0-42)

TAK: Takayasu arteritis; GC: glucocorticoid; CYC: cyclophosphamide; SD: standard deviation.

enrolled in the cross-sectional study. All patients fulfilled the proposed classification criteria of the American College of Rheumatology (ACR) 1990 for Takayasu's arteritis (18). Fifty-one age- and sex-adjusted healthy controls (HC) (45 female, 6 male) were recruited from the hospital staff. The study was approved by the Local Ethical Committee and written informed consent was provided from all participants. Subjects under the age of 18 and who is not being able to give informed consent were excluded. All patients underwent eye examination, vascular imaging, echocardiography and bone densitometry. Evaluation of clinical, angiographical and treatment characteristics and damage items of VDI and SF-36 scoring were done into a standardised protocol. Disease activity and quality of life (QoL) were evaluated by Kerr criteria (18) and SF-36, respectively. Active disease in TAK was considered if the patient presented with new onset or worsening of two or more features of TAK, including systemic constitutional features in the absence of other causes, elevated erythrocyte sedimentation rate, features of vascular ischaemia or inflammation, or typical angiographic features. Remission is defined as the complete resolution or stabilisation of all these features. Clinical and laboratory features were evaluated by one of the investigators of the each participating centres. Two investigators (SK, AO) reviewed the overall VDI and SF-36 paper forms, at the end of the study. TAK patients were stratified according to the disease activity as follows: Patients having persistent disease activity ≥6 months despite treatment (≥1 DMARD and ≥10 mg/d prednisolone as maintenance after remission induction with 0.5–1 mg/kg/d along with methotrexate and/or azathioprine) were accepted as resistant (r-TAK). Resistant TAK patients were compared to non-resistant (nr-TAK) group. The angiographic findings of TAK cohort were classified according to the proposal of "International Conference on TAK", in Tokyo, in 1994 (19).

QoL

QoL was evaluated with a validated Turkish translation of the SF-36 (20). The SF-36 is a generic measure containing 36 items that assess QoL in eight health dimensions: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE) and mental health (MH). On the basis of these separate subscales, physical (PCS) and mental component summary scores (MCS) were calculated. The scales and summary scores range from 0 to 100, with higher scores indicating better QoL (15, 21, 22).

Table II. Distribution of organ-system damage based on VDI in 165 TAK patients.

Organ system	n=165 (%)
Musculoskeletal	50 (30)
Skin/Mucous membranes	2 (1)
Ocular	44 (27)
Ear Nose and Throat (ENT)	3 (2)
Pulmonary	7 (4)
Cardiovascular	85 (52)
Peripheral vascular	160 (97)
Gastrointestinal	0
Renal	10 (6)
Neuropsychiatric	27 (16)
Other	19 (11)

Values are given as numbers of patients (%).

VDI

VDI has been developed to assess disease and treatment-related damage in systemic vasculitides. The VDI scores were calculated for each patient by physical examination, laboratory analysis, eye examination, echocardiography and bone densitometry data.

Statistical analysis

The VDI and SF-36 scores of r-TAK and nr-TAK patients were compared and the correlation between VDI scores and disease duration, cumulative GC, cyclophosphamide (CYC) treatment duration and doses, and mental (MCS) and physical (PCS) component summary scores of SF-36 were analysed. Analysis for normally distributed variables was performed by Student's *t*-test and by Pearson's correlation coefficient, whereas the analysis of non-normally distributed variables were done using Mann-Whitney U-test and Spearman's correlation coefficient. A multivariate, linear regression analysis was performed to determine the factors independently associated with VDI, PCS and MCS. The factors used in this multivariate analysis for VDI were sex, age, disease duration (months), cumulative corticosteroid dose (grams), and resistance. For PCS and MCS, VDI was also evaluated as an additional risk factor.

Internal consistency of the HAQ and SF- 36 were evaluated by using Cronbach's alpha test (each subscale against the HAQ total score). VDI scores according to the disease resistance and poor QoL (MCS and PCS scores <50) were also compared. All statistical analyses were performed using the

Table III. Damage items according to the VDI in 165 TAK patients damage.

Damage Items	Total n=165 (%)
Major vessel stenosis[1]	139 (84.2)
Absent pulses in one limb[1]	116 (70.3)
Claudication >3 months[1]	102 (61.8)
Diastolic BP≥95 or requiring anti-hypertensives[1,2]	74 (44.8)
Osteoporosis/vertebral collapse[2]	37 (22.4)
Valvular disease[1]	32 (19.4)
2nd episode of absent pulses in one limb[1]	23 (13.9)
2nd cerebrovascular accident[1]	21 (12.7)
Cataract[2]	21 (12.7)
Retinal change[1]	16 (9.7)
Visual impairment/diplopia[1]	14 (8.5)
Gonadal failure[2]	12 (7.3)
Significant muscle atrophy or weakness[1,2]	10 (6.1)
Cognitive impairment[1]	9 (5.5)
Angina angioplasty[1]	9 (5.5)
Myocardial infarction[1]	8 (4.8)
Pulmonary hypertension[1]	7 (4.2)
Cerebrovascular accident[1]	6 (3.6)
Diabetes[2]	6 (3.6)
Estimated/measured GFR ≤50%[1]	5 (3)
Proteinuria ≥0.5g/24hr[1]	5 (3)
Avascular necrosis[2]	5 (3)
Peripheral neuropathy[1]	4 (2.4)
Cutaneous ulcers[2]	3 (1.8)
Cardiomyophathy[1]	3 (1.8)
Malignancy[2]	3 (1.8)
Deforming/erosive arthritis[1]	-
Optic atrophy[1]	2 (1.2)
Cranial nerve lesion[1]	-

Values are given as numbers of patients (%).
[1]Disease-related damage. [2]Treatment-related.

Table IV. Treatment features of 165 TA patients.

Treatment features	n (%)
Steroid+ immunosuppressives	142 (86%)
Methotrexate	104 (63%)
Azathioprine	45 (27%)
Cyclophosphamide	13 (8%)
Leflunomide	32 (19.3%)
Mycophenolate mofetil	14 (8.4%)
Methotrexate + Azathioprine	7 (4.2%)
Methotrexate + Leflunomide	12 (7.2%)
TNF-α inhibitors	10 (6%)
Tocilizumab	2 (1.2%)
Patients only using anti-aggregants	11 (6.6%)
Patients only using corticosteroids	8 (4.8%)
Patients followed without treatment	4 (2.4%)

SPSS 16 system (SPSS Inc, Chicago, Illinois, USA). A *p*-value <0.05 was considered statistically significant.

Results

Demographic and clinical features

Demographic, clinical, angiographical features, treatment characteristics, VDI items and scores are shown in Table I. The mean (± SD) age was 38.2±7.9 years (range 22–58 years) in HC. Cumulative median doses and median duration of GC and CYC were 6.9 g (0–45), 48 months (0–384) and 0 g (0–31.5), 0 months (0–42), respectively. Thirty-nine percent of TAK cohort had active disease and 35% was defined as r-TAK.

Damage features and contributors

Distribution of organ-system damage and damage items of VDI in 165 TAK patients are shown in Table II and Table III. All patients had disease-related (VDI ≥1) but only 39.3% had treatment-related damage. The most frequent disease-related damage was peripheral vascular while osteoporosis and cataract were the main treatment-related damage items. Cumulative VDI score was found as 4 (1-12), which was mostly related to the disease itself 4 (1-10). VDI scores were found to be correlated with disease duration (p<0.01, r= 0.25), cumulative GC dose (p<0.01, r= 0.19), CYC (p=0.02, r= 0.17) and duration (p<0.01 r= 0.29) of GC. VDI scores in r-TAK patients were significantly higher than nr-TAK patients [5 (2–12) *vs*. 3 (2–10), p<0.001,)]. A significantly higher cumulative meadian dose of GC was found in r-TAK than nr-TAK patients [11g (0–45) *vs*. 5.7 g (0–43), p=0.006]. Treatment features of the patients are listed in Table IV.

SF-36 scores, resistant disease and VDI

All scores for SF-36 components, but RE and MCS were significantly lower in TAK in comparison to HC (Fig. 1). The SF-36 subscales showed high internal consistency with a Cronbach's alpha value of 0.93 (range 0.90–0.93), indicating a high reliability of the measure in our cohort. MC and PC scores lower than 50 were found in 115 (70%) and 132 (80%) TAK patients, respectively. SF-36 scores except PF and RE components were significantly lower in r-TAK subgroup when compared to nr-TAK (Fig. 2).

There was a negative correlation between VDI scores and MCS (p=0.003, r=-0.23) and PCS (p<0.001, r=-0.34). The higher VDI scores were detected in the subgroup of patients who had low PCS (<50) [5 (1–12) *vs*. 2 (1–6) p<0.001)].

Linear regression analysis revealed that resistance, cumulative corticosteroid dose, age, and disease duration were independently related with VDI (Table V). In the model of multivariate linear analysis for PCS, we observed that age and increase in VDI scores were related to significant decrease in PCS and for MCS model, increase inVDI was the only factor associated to MCS decrease in TAK patients (Table VI).

Discussion

To our knowledge, there is no reported study assessing the damage related to TAK itself or treatment. In this retrospective cross-sectional study, the extent and pattern of irreversible organ damage in patients with TAK was estimated using a validated clinical instrument, VDI. The results of the present study showed that increase in VDI was an independent risk factor for having a poorer quality of life represented with a decrease in PCS and MCS.

In this regularly followed-up TAK cohort with a mean disease duration of almost 6 years, high VDI scores were observed which could be attributed to the disease burden. Besides that, resistance, cumulative corticosteroid dose, age, and disease duration were found to be independently related with VDI which supports the importance of disease burden in TAK patients. The high percentage of resistant cases (40%) might possibly have a role on both disease and treatment-related damage. Disease duration seemed to have a contribution to damage. Peripheral vascular damage was found in almost all patients. "Major vessel stenosis", "absent pulse in one limb" and "claudication >3 months" items under the "peripheral vascular damage" category in VDI were marked concomitantly in two thirds of patients which constitute the majority of mean damage scores in TAK cohort. Stroke and symptomatic coronary artery disease were reported as 10–20% and 10–30%, respectively, in different TAK series (23-25). Myo-

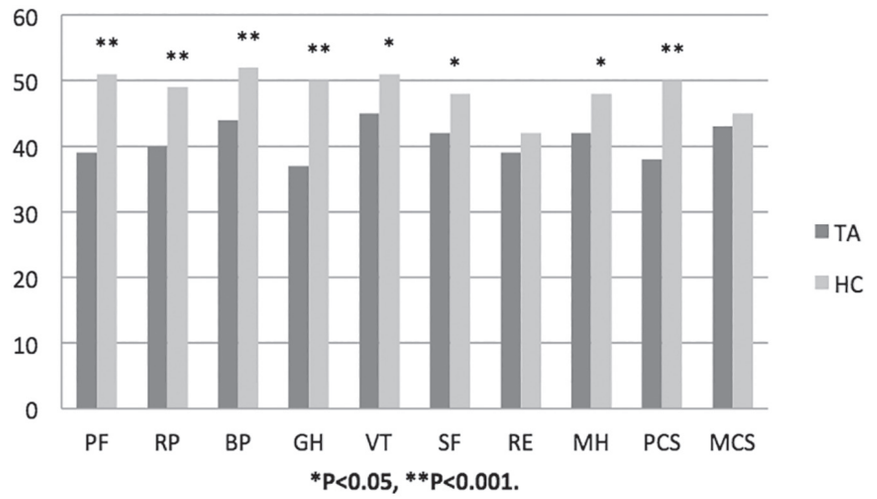

Fig 1. Short-Form 36 scores of TAK patients and healthy controls.
PF: physical functioning; RP: role physical; BP: bodily pain; GH: general health; VT: vitality; SF: social functioning; RE: role emotional; MH: mental health; PCS: physical component summary; MCS: mental component summary.

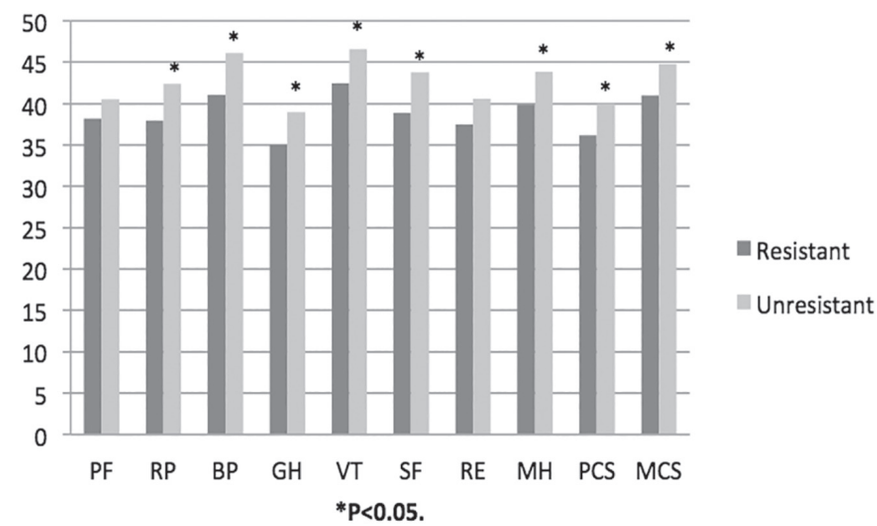

Fig 2. Short-Form 36 scores of each component in treatment-resistant and non-treatment-resistant patients.
PF: physical functioning; RP: role physical; BP: bodily pain; GH: general health; VT: vitality; SF: social functioning; RE: role emotional; MH: mental health; PCS: physical component summary; MCS: mental component summary.

cardial infarction and cerebrovascular event were infrequent (<5%) damage items in our cohort. The incidence of pulmonary hypertension (PAH) was also rare (<5%) when compared to 12-13% rate of PAH in different TAK cohorts including our national cohort (2, 26). This discordance may happen due to different approaches for the diagnosis of PAH. In this study, we diagnosed PAH in the presence of pulmonary artery pressure higher than ≥30 mmHg even in the absence of clinical symptoms and pulmonary function abnormalities. Severe organ damage (VDI>5) was not as frequent as small-medium-sized vasculitides (27-30), yet the mean cumulative damage scores of our TAK cohort was found as still remarkably high.

Cataract and osteoporosis, related to GCs, were the most frequent treatment-related items observed in our cohort. Though, a weak correlation was found between cumulative dose and duration of GC and damage.

CYC, as a drug having well-known potential toxic side effects, was not a confounder of treatment-related damage, probably due to its limited usage in TAK. In our cohort, higher VDI scores in resistant cases seem to occur on the basis of disease activity and higher GC exposure.

In this study, we evaluated the impact of damage in QoL by using a validated tool in TAK patients. All scores of SF-36 subscales were less than HC, reaching statistical significance, except RE and MCS. Majority of the cohort had poor quality of life. Turkish version of SF-36 was previously validated in both Turkish patients and healthy controls (20). SF-36 were previously used in different TAK cohorts from Turkey and the US (15-17). Majority of SF-36 components were found to be worsened in TAK patients comparing to both healthy and diseased controls representing peripheral vascular disease.

In this study we also observed that increase in VDI scores was independently related to decrease in PCS and MCS. Additionally, age was found to be another risk factor for PCS decrease in TAK patients. Yilmaz *et al*. reported significantly lower mental and physical summary scores of SF-36 for all subscales in TAK comparing to healthy controls. TAK patients with functional disability, anxiety and depression displayed worsened SF-36 scores, in this study. In another study from Turkey, by Akar *et al*., physical and mental health summary scores and all SF-36 subscales, except for social functioning, were found to be significantly lower in patients with TA than healthy controls but not in AS and RA patients. In a large US TAK cohort being compared with both age-matched healthy population and diseased controls with diabetes mellitus, hypertension, and coronary artery disease, lesser (SF-36<50) PCS and MCS summary scores were reported, as well. Damage have a negative impact on quality of life indicating through a weak correlation with PCS and moderate correlation with MCS. Resistant disease demonstrated worse scores in almost all SF-36 subscales which may possibly reflect the disease severity.

To our knowledge, this is the first study that both damage and QoL were investi-

Table V. Multivariate linear regression analysis of factors related to VDI.

	B	95% Confidence Interval	*p*
Age	0.30	0.002-0.058	**0.033**
Sex	-0.162	-1.186-0.832	0.748
Disease duration	0.004	0.000-0.008	**0.037**
Cumulative dose of corticosteroids (gr)	0.048	0.014-0.083	**0.006**
Disease resistance	1.362	0.708-2.017	**0.0001**

VDI: vasculitis damage index.

Table VI. Multivariate linear regression analysis of factors related to PCS and MCS.

	B	95% Confidence Interval	*p*
PCS			
Age	-0.195	-0.345 to -0.046	**0.011**
Sex	0.508	-4.891-5.907	0.853
Disease duration	0.016	-0.005-0.038	0.138
Cumulative dose of corticosteroids (gr)	-0.021	-0.207-0.165	0.820
Disease resistance	-1.863	-5.495-1769	0.313
VDI	-1.604	-2.446 to -0.762	**0.0001**
MCS			
Age	-0.042	-0.184-0.100	0.556
Sex	-0.018	-5.138-5.101	0.994
Disease duration	0.017	-0.003-0.038	0.098
Cumulative dose of corticosteroids (gr)	-0.032	-0.208-0.145	0.723
Disease resistance	-2.500	-5.945-0.944	0.154
VDI	-0.920	-1.718 to -0.121	**0.024**

PCS: physical component summary; MCS: mental component summary; VDI: vasculitis damage index.

gated with the validated tools in a large cohort of TAK patients. This study has some limitations. First, cross-sectional design is the major limitation of this study. Secondly, the lack of validated tools to definitely distinguish active disease from refractory disease activity may also be questioned. However, this data demonstrated the characteristics and relationship of damage and QoL in a long-term followed-up TAK cohort and it may give insight for further prospective studies. Disease-related damage mainly caused by peripheral vascular involvement was more predominant than treatment-related damage without being reaching the level of severe damage scores, but contributing to poor QoL. There is still an unmet need for better diagnostic and treatment strategies achieving low damage and high QoL scores in TAK. Therefore, close monitoring of disease activity/progression and a comprehensive disease control in TAK may contribute to prevent the occurrence of permanent damage and deterioration in the quality of life.

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