Imaging is the major determinant in the assessment of disease activity in Takayasu's arteritis

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ABSTRACT

Objective. *There are no valid follow-up parameters in the assessment of disease activity in Takayasu's arteritis (TAK). We investigated the impact of vascular imaging in the assessment of disease activity.*

Methods. *Patients with TAK who fulfilled the ACR criteria were included. Physician global assessment (PGA), the criteria defined by Kerr et al. and the Indian Takayasu Clinical Activity Score (ITAS2010) were evaluated. Patients were followed up using 3-6 monthly B-mode/Doppler ultrasonography (US) and 6-12 monthly magnetic resonance imaging/angiography (MRI/MRA). Active disease according to vascular imaging (Rad-Active) was defined based on the presence of any of the 3 parameters: (1) new vessel involvement by any imaging technique; (2) an increase in vessel wall thickness on US compared to previous one; (3) the presence of mural contrast enhancement/oedema on MRI/MRA. The agreement of Rad-Active with other disease activity indexes was studied. Furthermore, ITAS-A-Rad index was developed by combining the vascular imaging with ITAS-A.*

Results. *A total of 410 visits in 52 patients were evaluated. The agreement was found to be 76% (κ: 0.52) between Rad-Active and PGA; 83% (κ: 0.57) between Rad-Active and Kerr's criteria. Both the agreements of ITAS2010 and acute phase reactants with PGA (69%, κ:0.38 and 60%, κ:0.22, respectively) and also Kerr's criteria (78%, κ:0.49 and 42%, κ:0.05, respectively) were lower compared to those of Rad-Active. Mean ITAS-A-Rad scores were higher in visits with active disease according to PGA and Kerr's criteria.*

Conclusion. *The results of this study suggest that the vascular imaging should be included in the assessment of disease activity in TAK.*

Introduction

Takayasu's arteritis (TAK) is a granulomatous large-vessel vasculitis (LVV) that mostly involves the aorta and its proximal branches, and less commonly the pulmonary arteries (1). Narrowing, occlusion, and aneurysm of the involved large vessels may cause ischaemic symptoms in the later stages of the disease (2).

The close follow-up of disease activity is great of importance because of the intensive treatment needed during the active periods of TAK. However, currently there is no 'gold standard' in the assessment of disease activity. Acute-phase reactants (APRs), such as erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) levels may increase due to inflammation, but they are often not well correlated with disease activity (3).

Vascular imaging is essential in the diagnosis and monitoring of disease activity in TAK, but the issues of its modality and utility remain controversial. Conventional digital subtraction angiography (DSA) seems to have been replaced by the new techniques such as magnetic resonance (MR) angiography, computer tomography angiography (CTA) and ^{18}F-flurodeoxyglucose positron emission tomography (^{18}F-FDG-PET-CT) (4). B-mode/Doppler ultrasonography (US) is well correlated with angiography and can detect disease involvement in arteries with high sensitivity and specificity, except deeper vessels (5).

In 1994, Kerr *et al*. defined active disease as the criteria of constitutional symptoms, new bruits, and increased APRs or new angiographic features (6). This criteria set was mostly used as the disease activity criteria for TAK in studies (7). The latest developed index, the Indian Takayasu Clinical Activity Score (ITAS2010) is weighted

for vascular items and has been further combined with either APRs for more comprehensive measurement of disease activity (ITAS-A) (8).

In a previous Turkish study (9), we showed that there was a moderate correlation between Physician Global Assessment (PGA) and ITAS2010, and also ITAS-A. However, there were considerable numbers of patients accepted as having active disease based on their positive imaging findings although their ITAS2010 and ITAS-A scores were negative. In the present study, therefore, we aimed to investigate the impact of the vascular imaging in the assessment of disease activity in TAK.

Methods

Patients

Patients with TAK who were followed up at Dokuz Eylul University Medical Faculty were included in the study. Detailed medical history was obtained and a full physical examination was performed in each patient.

Ethics

The study was performed according to the Declaration of Helsinki and all subjects gave informed consent before participation. Dokuz Eylul University Hospital Ethics Board approved the study (no.: 2014/23-17).

Assessment of disease activity in patients with TAK

Disease activity was measured using various tools, including APRs (ESR and serum CRP), radiologic parameters, Kerr's criteria (active disease: >2 criteria) (6), PGA (active and inactive disease) (10), and the ITAS2010/ITAS-A scores (8).

The ITAS2010 forms were completed directly during routine visits after 2013, and retrospectively using our TAK registry for visits before 2013. Active disease was defined as >1 for ITAS2010 and >4 for ITAS-A subsets (9).

Imaging

According to the TAK follow-up protocol of the Rheumatology and Radiology Board of our hospital, the patients with TAK were followed using 3–6 monthly US examinations and 6–12 monthly magnetic resonance imaging (MRI) examinations with MRA (11).

Bilateral carotid, subclavian, upper, lower extremity, renal and mesenteric arterial and abdominal aorta US examinations were performed in all patients with TAK. All US examinations were performed by the same radiologist, as previously described using a scanner (HDI-5000; Advanced Technology Laboratories, Bothell, WA, USA and HD-11; Phillips Medical Systems, Bothell, WA, USA) equipped with 12.5-MHz and 7.5-MHz linear array imaging probes. An intima media thickness of at least 0.8 mm was defined as increased wall thickening on US (12).

MR studies were performed using a 1.5-T MRI scanner with an 8-channel body coil (Achieva 1.5T; Philips Healthcare, Best, Netherlands). MR studies included examinations of the aorta and its major branches from the carotid bifurcation to the infrarenal aorta and brachial arteries in coronal acquisitions (2D Bolus Trak: 80 mm, TR: 4, TE: 0.871 ms, FOV: 530 and 3D Bolus Trak HR cor slice thickness: 3.2mm, TR: 5.02 ms, TE: 1.41 ms, FOV: 400 mm). For supraaortic branches, T1W fat-suppressed black-blood, non-contrast and contrast-enhanced (axial slice thickness 8 mm, TR: 2000, TE 8.6 ms, FOV 350 mm) images were taken. T1-weighed MRI sequences with black blood imaging were taken to evaluate mural inflammation. We graded mural inflammation findings to define active disease: mural contrast enhancement/oedema (13).

In the follow-up, we performed DSA for patients only when needed for endovascular interventions. The vascular radiologist, who was blinded to clinical data, interpreted all the imaging examinations.

We categorised the patients as having radiologic active disease (Rad-Active) based on the imaging examinations if any of the following findings were positive: (1) New vessel involvement including chronic changes such as stenosis, obstruction and aneurysm on MRI/MRA and/or US; (2) an increase in arterial wall thickness on US compared to the previous one; (3) the presence of mural contrast enhancement/oedema on MRI/MRA.

Development of the 'ITAS-A-Rad' composite index

A scoring was done based on the imaging findings: 5 for a new vessel involvement on MRI/MRA and/or US and 3 for each item 2 and 3 above. These scores then combined with ITAS-A to obtain a composite disease activity index, named as ITAS-A-Rad. Active disease was defined as the ITAS-A-Rad ≥5 points. Therefore, the presence of a new vessel involvement alone was sufficient to meet the criteria for active disease (Table I).

In the determination of cut-off value for the ITAS-A-Rad score, receiver operating characteristics (ROC) curve analysis was used. The ITAS-A-Rad ≥5 points was considered acceptable with sensitivity of 93% and specificity of 79% for active disease when Kerr's criteria was used as the gold standard.

The rheumatologists scored the visits using ITAS-A-Rad while having all clinical, imaging, and laboratory data.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Science 13.0 (SPSS) statistics program. Results were expressed as mean with standard deviation (SD) or median with interquartile range (IQR) according to the distribution of the data. The Mann-Whitney U-test was performed for comparisons of the data. The percentages of exact agreement and Kappa statistics were used for the assessment of convergence between disease activity parameters. The responsiveness to change was examined through serial ITAS-A-Rad score assessments and shown in a line chart.

Results

A total of 52 patients with TAK [median (IQR) age: 53 (17) years, female: 92.3%] were included in the study. The mean (SD) disease duration was 3.5 (6.2) years. Of them, 34 (65.4%) were newly diagnosed during the study.

Total 410 visits in 52 patients were evaluated. Patients were followed up for 11 serial visits. The mean (SD) follow-up duration was 6.4 (2.9) years. After the 6th visit, the number of patients decreased to 32 (61.5%). 15 patients (28.8%) completed 11 serial visits.

Table I. The definition of ITAS-A-Rad score.

Definition	Method		Score
ITAS2010	Clinical		≥0
ITAS-A	ITAS2010 + acute phase reactant (ESR or CRP)	ESR	ITAS score plus 0 for ESR<20, 1 for 21-39, 2 for 40-59, 3 for >60 mm/h
		CRP	ITAS score plus 0 for CRP≤5, 1 for 6-10, 2 for 11-20, 3 for >20mg/L
ITAS-A-Rad*	ITAS-A + Rad	New vessel involvement by any imaging method	ITAS-A score plus 5
		Progression of vessel wall thickness on B-mode US	ITAS-A score plus 3
		Presence of mural contrast enhancement/oedema on MRA/MRI	ITAS-A score plus 3

*Active disease: ITAS-A-Rad ≥5.

Table II. Agreements between the disease activity scores.

Index	PGA	Kerr *et al*.'s criteria
APRs	60%, κ:0.22	42%, κ:0.05
ITAS 2010	69%, κ:0.38	78%, κ:0.49
ITAS-A	68%, κ:0.34	87%, κ:0.61
Rad-Active	76%, κ:0.52	83%, κ:0.57
ITAS-A-Rad	72%, κ:0.50	82%, κ:0.56

Cohen's kappa test (κ:0-0.20 none to slight, κ:0.21-0.40 fair, κ:0.41-0.60 moderate, κ:0.61-0.80 substantial, κ:0.81-1.00 perfect agreement).

47 patients (90.3%) used glucocorticoid treatment across the study period. The patients were on disease-modifying anti-rheumatic drugs (DMARDs) during the majority of visits (92.7%). Only 7 patients used anti-tumour necrosis factor-α treatment during the follow-up.

Among the 410 visits of the 52 patients with TAK, radiologic assessment was performed in 359 (US in 271 and MRI/MRA in 190). Patients were categorised as having active disease in 194 visits (47.4%) according to PGA and 72 visits (17.5%) according to Kerr's criteria. The agreement between them was fair (66%, κ: 0.29). Radiologic disease activity parameters were positive in 105 out of 359 visits (29.2%). The total agreement of Rad-Active with Kerr's criteria and PGA was found to be 83% (κ: 0.57) and 76% (κ: 0.52), respectively (Table II).

There were 9 visits with new vessel involvement (on US in 6 and MRI in 3) across the follow-up period. All these visits included patients with active disease based on both PGA and Kerr's criteria, although 4 patients had normal APR levels. Other active visits according to the imaging (n=96) were based on US and MRI/MRA that showed the increased wall thickness (n=58) and contrast enhancement/oedema (n=57), respectively.

The agreement between ITAS2010 and PGA was fair (69%, κ: 0.38). When APR was added (ITAS-A), it did not improve (68%, κ: 0.34). However, the agreement between ITAS-A-Rad and PGA (72%, κ: 0.50) and also Kerr's criteria (82%, κ: 0.56) was found to be moderate. Interestingly, when only US (ITAS-A-US) or only MRI/MRA (ITAS-A-MR) was used, the agreement with PGA remained almost unchanged (73%, κ: 0.45 and 76%, κ: 0.52, respectively) (Table II). Although the agreements of ITAS2010 and ITAS-A with Kerr's criteria were also found to be moderate (78%, κ: 0.49 and 87%, κ: 0.61 respectively) (Table II), there were 31 visits with active disease based on ITAS-A-Rad, but inactive disease based on both ITAS2010 and ITAS-A scores.

The mean (SD) ITAS-A-Rad scores were significantly higher in visits with active disease according to both PGA [7.83 (6.30); $p<0.001$] and Kerr's criteria [13.37 (6.00); $p<0.001$] compared to visits with inactive disease [1.80 (2.50) and 2.75 (3.20), respectively].

When responsiveness to change of ITAS-A-Rad score was evaluated in serial visits, it was found that the mean score value was discriminative for disease activity according to PGA in 9 of 11 visits (Table III and Fig. 1).

The highest mean ITAS-A-Rad scores were observed in the first visit group that included many patients with new diagnosis. All 34 newly diagnosed patients had active disease based on ITAS-A-Rad scoring. ITAS-A-Rad scores decreased significantly in the following visits after treatment. In the first visit, there were 22 patients with an increased vessel wall thickness on US. A regression in the vessel wall thickness was observed in 7 patients and stable findings with treatment in the remaining 15 during the second visit.

Forty-nine of 52 patients had at least one finding of chronic changes in their initial visits. Only 3 patients were diagnosed through acute lesions only and they showed no progression to chronic changes under the treatment. The retrospective evaluation of serial examinations showed progression from acute to chronic lesions in the 6 patients (11.5%) although they were properly treated.

Discussion

This long-term observational study showed that radiologic disease activity parameters obtained by using US and MRI/MRA correlated well with Kerr's criteria and PGA in patients with TAK. This was a considerable result,

Table III. ITAS-A-Rad scores in patients with active and inactive disease in serial visits.

Visit no	ITAS-A-Rad Score Mean (SD)		
	PGA active	**PGA inactive**	***p***
1	15.26 (6)	5.25 (4.9)	0.002*
2	6.23 (4.6)	1.92 (3.8)	0.005*
3	5.11 (3.3)	1.40 (1.63)	<0.001*
4	4.11 (2.47)	1.60 (1.72)	0.001*
5	6.36 (5.6)	1.36 (1.7)	<0.001*
6	3.20 (2)	2.95 (3.9)	0.29
7	4 (2.3)	1.76 (2.7)	0.041*
8	5.3 (3.8)	1.3 (1.77)	0.003*
9	4.33 (6.02)	1.21 (2.3)	0.02*
10	6.67 (4.5)	1.5 (2.3)	0.005*
11	4 (2.7)	1.10 (0.99)	0.028*

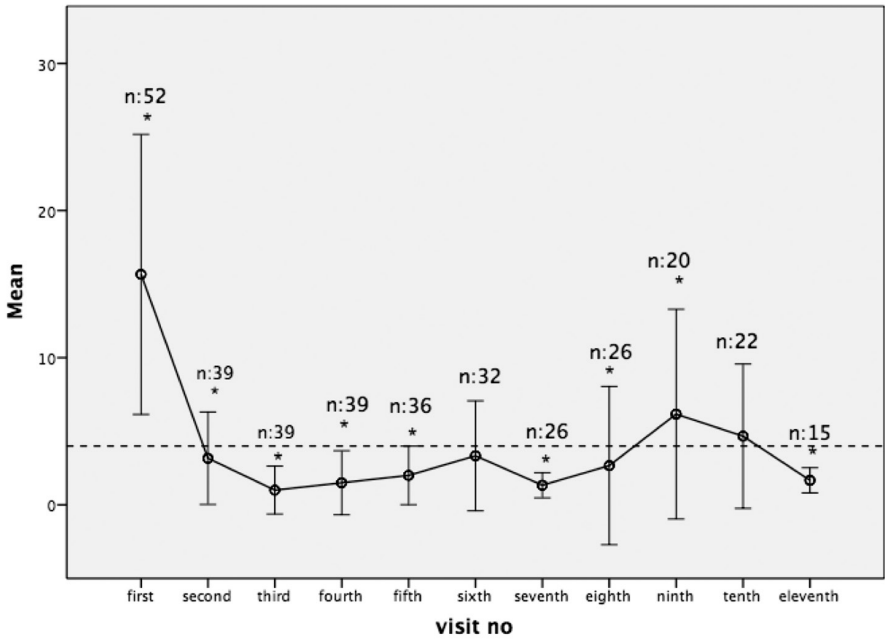

Fig. 1. Response to change; mean ITAS-A-Rad scores in serial visits.
Line chart: vertical label: mean ITAS-A-Rad scores, horizontal label: visit number.
Error bars: 95% confidence interval (CI); n: number of patients.

as the assessment of disease activity in TAK was one of the major challenges for physicians and there was no gold standard in the monitoring (4, 14).

Patients with TAK who have no signs or symptoms of active disease might have evidence of radiologic inflammation. US is an excellent imaging modality in TAK because it can reveal both vessel wall and lumen changes, it is also informative for early arterial wall changes. Diffuse and homogeneously thickened vessel wall (vasculitic pattern) is a reliable indicator for the diagnosis of TAK and can be differentiated from the atherosclerotic pattern (15). Moreover, US is a noninvasive technique and capable of examining several vascular levels in a single session, except some deeper vessels. Another advantage of US is its ability to take follow-up scans to monitor vessel involvement over time in TAK (16). A substantial degree of operator dependency may be a limitation; however, in this study, the same experienced radiologist performed all the US evaluations. Several studies reported that patients with TAK with active disease had increased wall thickening on US compared with inactive patients (16-18). Wall thickening may persist to some degree in some cases even after the patient achieved an inactive state (19). Therefore, we took into account only new or worsening vessel wall thickness within the past 3-6 months in the assessment of Rad activity in this scoring system.

We also performed MRI/MRA in all patients, combined with US, because of its superiority for imaging some deeper vessels. Monitoring the deeper vessels is important in patients with TAK, because of the considerable prevalence of their involvements (20). In the MR examinations, we accepted the presence of mural contrast enhancement/oedema as a disease activity indicator, independently from the previous MRI. By using serial periodic MR examinations, it is possible to evaluate not only the mural contrast enhancement/oedema but also the new stenosis since its first appearance. We only scored vascular stenosis that developed newly on MRI/MRA. This imaging is necessary because not always a new stenosis can induce a claudication, decrease or disappearance of the pulse, bruit, and asymmetrical pattern of pressure at the level of the upper and lower limbs. Thus imaging alone can detect a change in the therapeutic strategy. In the evaluation of MR examinations, the intra-rater (AG) and inter-rater (AG and OA) agreement was found to be 88% (κ: 0.77) and 89% (κ: 0.80), respectively.

There are two main concerns related to imaging modalities in TAK in the assessment of disease activity. The first is the ability of differentiation between activity and damage. Increased arterial wall thickness on US and arterial wall oedema on MRI/MRA was considered to reflect active disease. A recent study that compared findings between MRI/MRA and PET-CT supported that contrast enhancement/oedema on MRA reflected active disease because they were associated with FDG uptake, whereas stenosis, aneurysm and occlusion on MRA were not (21). These latter changes may reflect damage (22, 23). Another concern about imaging is responsiveness to change with treatment. Several studies and case reports showed that increased vessel wall thickness might regress when patients achieve an inactive state with treatment

in TAK (24-26). We also documented ultrasonographic improvement with treatment in the patients who had active disease before.

Recently, the European League Against Rheumatism (EULAR) published recommendations for the use of imaging in large-vessel vasculitis (27). The authors suggested that MRI should be the first imaging test used to investigate mural inflammation and/or luminal changes in the diagnosis of TAK, assuming high expertise and prompt availability of the technique. They also suggested PET-CT, CT and/or US might be used as alternative modalities in patients with suspected TAK.

The recent EULAR guideline also recommended imaging in the follow-up of disease activity, but only in patients with clinically and biochemically active disease (27). However, several histopathologic studies demonstrated active arteritis in >40% of patients who were thought to be in clinical remission (6, 28, 29). Therefore, compared with clinical assessments and APRs, new vessel involvement is usually accepted to be the most indicative for ongoing active disease in TAK. During the follow-up of our study, there were 9 visits including patients with new vessel involvement and active disease based on both PGA and Kerr's criteria. But 4 of these patients had normal APR levels. In a recent review that discussed the discrepancies between systemic and vascular wall inflammation (30), Keser *et al*. suggested that systemic and vascular inflammation might occur by different cytokine pathways, so APRs could sometimes be detected as normal despite ongoing vascular inflammation in TAK. Also a study suggested that TAK patients with stable disease might have a smoldering inflammatory response with cytokine involved in Th17 response (31). In this patient group, which has vascular inflammation predominantly, imaging may be the only method to detect disease activity because histopathologic evaluation is mostly impossible.

The limitations of this study are that PET-CT and CTA were not included. PET-CT might have been useful, especially in the early diagnosis of TAK, but its reproducibility is quite lower because of its high cost and limited availability (32, 33). CTA is widely available and also has ability of monitoring both vessel wall and lumen in terms of disease activity (34). Also the chronic changes as stenosis might be better visualised by CTA (5, 35). But both PET-CT and CTA are associated with significant radiation exposure as a condition limiting serial imaging at certain intervals. Therefore, we used them rarely in the monitoring of the disease activity in our TAK patients.

In this study, we also defined a new composite score, ITAS-A-Rad, to assess disease activity in TAK. It was developed based on ITAS2010 and included radiologic disease activity parameters obtained using both US and MRI, as well as clinical measures and APRs. This long-term follow-up study demonstrated that ITAS-A-Rad was well correlated with PGA and also the Kerr's criteria. ITAS-A-Rad was also found to be discriminative for disease activity when its responsiveness to change was evaluated in serial visits.

ITAS2010 and ITAS-A were among the first validated assessment tools for monitoring TAK (8). A previous multicentre controlled study showed that they were discriminative for disease activity during follow-up compared with Kerr's criteria and had moderate agreement with PGA (9). ITAS2010 is the preferable clinical activity index in TAK because of proportionally weighted for vascular items. However, our previous study (9) showed that there were considerable numbers of TAK patients who were accepted as having active disease by their physicians because they had positive imaging findings despite having no active disease based on ITAS2010 and ITAS-A. It is well known that many patients with TAK in clinical remission may have evidence of ongoing vascular inflammation on imaging. Therefore, the extent of arterial involvement with vascular imaging is essential to monitor patients with TAK (36). In this study, we detected the major contribution of the Rad component while determining active disease in such a clinically silent patient group. There were considerable numbers of visits with active disease according to both the ITAS-A-Rad and PGA but without active disease based on both the ITAS2010 and ITAS-A.

In ITAS-A-Rad, we primarily aimed to assess the disease activity in each visit separately. The evaluation was not based on the score change in the follow-up; it was based on active or inactive disease represented by the total score at each visit.

In this scoring system, we included both US and MRI/MRA as the first-line imaging modalities, which are capable of evaluating both the arterial lumen and wall, in the diagnosis and also in the decision-making regarding disease activity in TAK. The combination of these two modalities allowed monitoring disease activity parameters in nearly all large arteries affected by TAK, without exposure to any radiation. This last issue is very important for the TAK population, which is mostly young and reproductive-age females (37).

In conclusion, this study suggested that vascular imaging should be included in the assessment of disease activity in TAK. Using vascular US in combination with MRI provides to determine active inflammation without missing any large arteries. The ITAS-A-Rad, a new modified ITAS2010 score including imaging items, may be used as a valuable follow-up measure in the assessment of disease activity in TAK. ITAS-A-Rad may also be useful in the monitoring response to treatment. A further prospective validation study in a new independent cohort is needed to confirm our results.

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