Assessment of Patients with Takayasu Arteritis in Routine Practice with Indian Takayasu Clinical Activity Score

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ABSTRACT. *Objective.* To assess the Indian Takayasu Clinical Activity Score (ITAS2010) in followup of Takayasu arteritis (TA).

Methods. ITAS2010 forms were filled in prospectively (n = 144). Clinical activity was assessed with physician's global assessment (PGA) and criteria defined by Kerr, *et al*.

Results. ITAS2010 was significantly higher in patients with active disease. Total agreement between ITAS2010 and PGA was 66.4%, and between ITAS2010 and Kerr, *et al* was 82.8%. During followup, 14 of 15 patients showing vascular progression with imaging were categorized as having inactive disease according to ITAS2010.

Conclusion. ITAS2010 was discriminatory for activity during the followup, but the agreement between PGA and ITAS2010 was moderate. Future work should include the incorporation of advanced vascular imaging and demonstration of ITAS2010 as a scalable measure and not simply a dichotomous measure of activity/flare versus remission. (J Rheumatol First Release July 1 2015; doi:10.3899/jrheum.140817)

Key Indexing Terms:
TAKAYASU ARTERITIS   ITAS2010   ACTIVITY   ASSESSMENT

Takayasu arteritis (TA) is a rare, chronic, large vessel vasculitis that predominantly affects the aorta, its major branches, and the pulmonary arteries[1]. Assessment of activity in TA is difficult and efforts to develop validated tools for research and clinical practice are continuing. The simple definition of "active disease" that was first defined by Kerr, *et al* (presence of constitutional symptoms, new bruits, acute-phase response, or new angiographic features) is commonly applied in studies of TA[2]. Although designed to apply to all vasculitides, the Birmingham Vasculitis Activity Score (BVAS) is validated for use only in small- and medium-vessel vasculitis. However, because most of the 11 organ systems in BVAS are not involved in TA, the value of BVAS is limited[3]. The disease extent index for TA (DEI.Tak) is an attempt to derive an activity/extent index based on the BVAS. DEI.Tak assesses activity/extent with only clinical findings, without a requirement for imaging techniques, but is not widely accepted[4,5].

Misra, *et al* developed and validated a new composite index — the Indian Takayasu Clinical Activity Score (ITAS2010) — for the clinical assessment of TA. ITAS2010 was again developed from the BVAS and is also weighted for vascular items[6]. In our study, we aimed to investigate ITAS2010 in a second population for the routine clinical

followup of patients with TA from Turkey to externally validate it as an assessment tool using physician's global assessment (PGA) as the gold standard.

MATERIALS AND METHODS

The study included 144 patients (age 40.9 ± 12.3 yrs, female/male: 128/16) fulfilling the American College of Rheumatology (ACR) criteria for TA[7] and followed in 8 centers in Turkey. The eligibility criteria for our study were the diagnosis of TA according to the ACR 1990 criteria, having sufficient data on acute-phase reactants (APR), vascular symptoms, physical examination, and PGA during the visit. The mean disease duration was 8.3 years (0–40). ITAS2010 forms were filled in routine visits prospectively, with intervals of at least 4–6 months, by including only new or worsening symptoms within the past 3 months, as suggested. In total, 289 visits from 144 patients were included. APR and progressions in imaging modalities (whenever available) were recorded. In experienced centers in Turkey, imaging for the followup of TA was performed as clinically required to assess active disease. Different imaging modalities according to the preferential approaches of individual centers were chosen. Positive imaging was defined as development of a new vascular involvement, progression in luminal vascular lesions, or increased vascular uptake in 18F-fluoro-deoxyglucose positron emission tomography (FDG-PET).

Active disease by PGA was defined by the attending physician as any new symptom that is associated with disease activity, such as malaise, weight loss, myalgia, dizziness, or claudication; new signs, such as hypertension, syncope, or bruits; or any elevation in acute-phase responses. PGA assessments were performed before imaging results were present.

ITAS2010 with APR (ITAS-A) was calculated combining ITAS2010-A [either erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)], as suggested by Misra, et al[6]. ITAS-ESR was calculated as ITAS plus 0 for < 20, 1 for 21–39, 2 for 40–59, and 3 for > 60 mm/h by Westergren method. ITAS-CRP was calculated as ITAS plus 0 for ≤ 5, 1 for 6–10, 2 for 11–20, and 3 for > 20 mg/l[6]. If both ITAS-ESR and ITAS-CRP were available, the higher score was accepted as ITAS-A. Active disease was defined as > 1 for ITAS2010 and > 4 for ITAS-A subsets. Patients were also evaluated by activity defined by Kerr, et al[2]. PGA was used as the gold standard activity definition in our study; however, if available, activity defined according to Kerr, et al was also used.

During the study period, oral methylprednisolone was given to 133 patients (91.7%). As additional immunosuppression (IS), 49 patients (34%) received azathioprine, 77 (53.5%) received methotrexate, 10 (6.9%) received leflunomide, 4 (2.8%) received infliximab, and 1 (0.7%) received mycophenolate mofetil therapy.

The study was performed according to the Declaration of Helsinki and all subjects gave informed consent before participation. Statistical data were performed with Statistical Package for the Social Sciences 16.0 (SPSS) program. Results were expressed as means and SD or as median (minimum–maximum) according to the distribution of data. Mann-Whitney U test, independent samples Student t test, Wilcoxon test, and chi-square test were used for comparisons of data. Spearman correlation test was used to analyze correlations. The percentage of exact agreement was calculated for clinical activity assessment tools. Kappa statistics (unweighted κ for dichotomous assessment) were also used for the assessment of convergence between ITAS2010, ITAS-A, Kerr, et al's criteria[2], and PGA.

RESULTS

Among the 338 visits of 144 patients, 289 visits were included in our study and 49 were excluded because of insufficient information about the presence and the duration of current symptoms and signs. According to PGA, patients were categorized with active disease in 129 visits (44.6%), whereas active disease was present in only 68 visits (23.5%) according to ITAS2010. In 140 visits, Kerr, et al activity definition was available and in 18 of these (12.9%), patients were categorized with active disease. In 8 of these 18 patients, imaging was available and showed a radiologic progression. ITAS2010, ITAS-ESR, ITAS-CRP, and APR were significantly higher in patients with active disease compared with those with inactive disease, defined with both PGA and Kerr, et al (Table 1). Distribution of ITAS2010 according to the PGA is given in Figure 1. ITAS2010 significantly correlated with both ESR (r = 0.230, p < 0.001) and CRP (r = 0.238, p < 0.001). As expected, ITAS2010 also significantly correlated with ITAS-ESR and ITAS-CRP (r = 0.975, p < 0.001 and r = 0.969, p < 0.001, respectively). While PGA significantly correlated with both ESR (r = 0.476, p < 0.001) and CRP (r = 0.292, p < 0.001), Kerr, et al showed a weak correlation only with ESR (r = 0.173, p = 0.04).

The total agreement between ITAS2010 and PGA was 66.4% (κ = 0.29), and between ITAS2010 and Kerr, et al, it was 82.8% (κ = 0.35). The total agreement between PGA and Kerr, et al was also moderate (70.7%, κ = 0.28). When APR was added, total agreement between PGA and ITAS-A did not improve much (67%, κ = 0.29). However, agreement was better with Kerr, et al (86.3%, κ = 0.35).

A step-up regimen increasing the IS dose or changing/adding new agents was chosen in 45 patients during the followup period. While 43 of these patients had active disease according to PGA (95.5%), only 33 patients had active disease with ITAS2010 (73.3%).

Forty-three patients were evaluated with imaging in the followup period [6 with FDG-PET, 23 with magnetic resonance (MR) angiography, 8 with vascular Doppler ultrasonography, 3 with computerized tomography (CT) angiography, and 3 with conventional angiography]. Vascular progression was observed in 15 patients (34.9%) with imaging. Only 1 patient showing progression with imaging was categorized as having inactive disease with PGA. However, 14 of 15 patients showing progression with imaging were categorized as having inactive disease according to ITAS2010, but accepted to be active with PGA. Imaging was significantly compatible with PGA (p < 0.001), but not with ITAS2010 (p = 0.953) for active disease (Table 2).

We also analyzed the data with an equal number of visits per patient to prevent any bias attributable to unequal visit numbers. When only 1 visit from each patient was analyzed (n = 144), ITAS2010, ITAS-ESR, ITAS-CRP, and APR were again significantly higher in patients with active disease compared with those with inactive disease, defined with both PGA and Kerr, et al (Supplementary Table 3 is available from the authors on request). The total agreement between ITAS2010 and PGA was 68% (κ = 0.336), and between ITAS2010 and Kerr, et al was 86.5% (κ = 0.622). The total agreement between PGA and Kerr, et al was also good (85%, κ = 0.660). When APR was added, total agreement between PGA and ITAS-A did not improve (66.5%, κ = 0.3). When

Table 1. Comparison of ITAS 2010, ITAS-ESR, and ITAS-CRP scores and APR between patients with active and inactive disease, defined according to PGA and Kerr, *et al*[2] in all visits. Values are mean ± SD [median (IQR)] or mean ± SD unless otherwise specified.

Variables	PGA			Kerr, *et al*		
	Active, n = 129	Inactive, n = 160	p	Active, n = 18	Inactive, n = 122	p
ITAS2010	3.1 ± 5.1 [0 (0–24)]	0.5 ± 1.7 [0 (0–15)]	< 0.001	5.6 ± 6.8 [2 (0–19)]	0.8 ± 2.1 [0 (0–15)]	< 0.001
ITAS-CRP	4.0 ± 5.3 [2.5 (0–24)]	0.8 ± 1.9 [0 (0–18)]	< 0.001	6.8 ± 6.8 [3.5 (0–22)]	1.4 ± 2.4 [0 (0–16)]	< 0.001
ITAS-ESR	4.3 ± 5.1 [2 (0–24)]	0.9 ± 2 [0 (0–18)]	< 0.001	5.9 ± 5.6 [3 (0–18)]	1.6 ± 2.4 [1 (0–17)]	< 0.001
ESR, mm/h	35.9 ± 21	17.8 ± 12.4	< 0.001	37.7 ± 18.4	26.5 ± 18.2	0.025
CRP, mg/l	13.2 ± 19.2	4.9 ± 5.6	< 0.001	12.5 ± 13.9 [11 (0.1–54.3)]	7.3 ± 9.6 [3.4 (0.2–58)]	0.06

ITAS2010: Indian Takayasu Clinical Activity Score; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; APR: acute-phase reactants; PGA: physician's global assessment; IQR: interquartile range; n: number of visits.
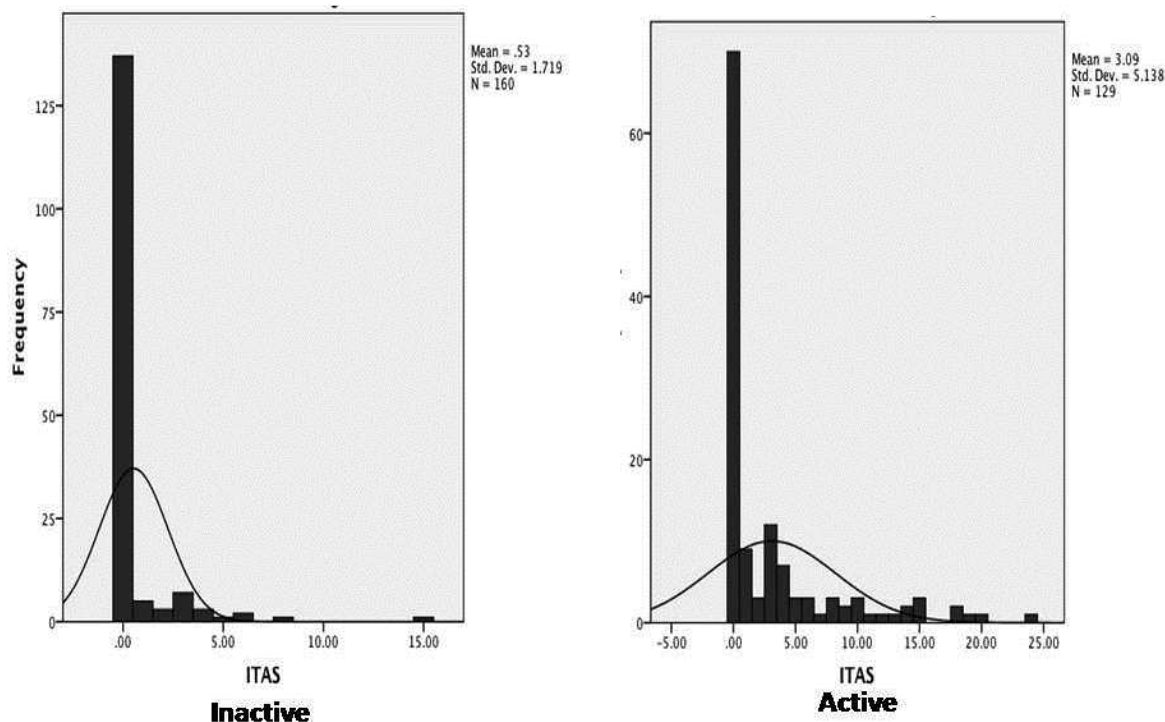

Figure 1. Distribution of ITAS2010 score according to physician's global assessment.

Table 2. Distribution of patients with active and inactive disease according to PGA and ITAS2010 in groups developing vascular progression with imaging. Values are n.

Variables		Progression+	Progression–
ITAS2010	Active	1	2
	Inactive	14	26
PGA	Active	14	8
	Inactive	1	20

PGA: physician's global assessment; ITAS2010: Indian Takayasu Clinical Activity Score.

the 170 visits of 85 patients (2 visits for each patient) were analyzed, results were again similar to the whole group (Supplementary Table 4 is available from the authors on request). The total agreement between ITAS2010 and PGA was 66.4% (κ = 0.326), and between ITAS2010 and Kerr, *et al* was 79.7% (κ = 0.333). The total agreement between PGA and Kerr, *et al* was also good (78.7%, κ = 0.508). When APR was added, total agreement between PGA and ITAS-A also did not improve (65.6%, κ = 0.311).

DISCUSSION

There is currently no gold standard for the assessment of disease activity in TA. PGA is widely used as the assessment tool in routine clinical practice and is based on clinical features, APR, and imaging abnormalities that are also reflected in the criteria defined by Kerr, *et al*[2,8]. Assessment

of APR is frequently advocated for disease assessment in TA, despite being shown to be neither sensitive nor specific enough to monitor disease activity[9]. Data coming from the new studies support that imaging with MR angiography and FDG-PET is also promising[1].

ITAS2010 and the composite score ITAS-A, including clinical features plus APR, are the first validated assessment tools for monitoring activity in TA[6]. In our present study, ITAS2010 had a discriminatory value in all visits for active disease, compatible with Misra, *et al*[6]. ITAS-ESR and ITAS-CRP scores were also significantly higher in patients with active disease and a significant correlation was also observed between APR and ITAS2010 in all visits. Misra, *et al* suggested that ITAS-A was comparable with ITAS-2010 regarding performance, but remained elevated in the followup period in spite of clinical response to induction therapy. Although CRP and ESR had weak correlations with ITAS2010, the authors made a further attempt to incorporate APR to the score (ITAS2010-A) by adding an extra 1–3 points for elevated ESR or CRP. This change resulted in higher ITAS2010-A scores in patients with both active and inactive disease. Further, when "response to change" was assessed by ITAS2010-A, patients still had a mean score of 4 at the third visit when they were deemed to be clinically inactive with PGA. That items on the ITAS2010 are still present even during apparent remission is problematic and illustrates the substantial difficulty in differentiating activity from damage because of nonvasculitis-related problems in TA[10].

In our study, the agreement between PGA and ITAS2010 was observed to be moderate (66.4%), similar to the original study. The total agreement between PGA and ITAS-A was not much better (67.1%). Both ITAS2010 and ITAS-A have better correlations with Kerr, *et al* (82–86%). ITAS2010 is based primarily on physical examination for new vascular signs. However, Grayson, *et al*, who investigated the association between physical examination and imaging data, showed that individual physical examination findings had poor sensitivity (14–50%), and even when used in combination, at least 30% of arteriographic lesions were missed[11]. Further in this context, ITAS2010 requires a score > 1 and ITAS-A > 4 as cutoffs for positivity, which might be too high for the assessment of "low disease activity." Physicians' general sense of "active disease," such as constitutional symptoms (malaise, weight loss) or dizziness, and some clinical features, such as systolic hypertension, score only 1 point in ITAS2010 and are below the threshold for active disease. Similarly, isolated APR elevations (1–3 points) without clinical features are not sufficient to define active disease by ITAS-A, whereas they may lead the physician for new imaging. In support of our results, we have recently demonstrated that PET was positive in 13 of 14 patients investigated for isolated APR without any clinical symptom or sign for at least 3 months[12]. Therefore, imaging methods such as CT and MR angiography that show both lumen changes and vessel wall enhancement and PET demonstrating vessel wall activity seem to support physicians' final decisions on therapy changes[13,14]. ITAS2010 was used in open-label case series of biological agents such as anti-tumor necrosis factor-α and antiinterleukin 6 therapies in TA[15]. However, because only 2 assessments were reported with the baseline visit highly elevated, whether ITAS2010 will be a suitable clinical tool to reflect response to biological treatments in longterm followup still needs to be clarified[16].

Major limitations of our study are the short followup duration and limited imaging data in our patient group. Preference of different imaging modalities according to individual protocols of study centers is also another limitation. In a slowly progressive disease such as TA, more followup duration is necessary to show individual changes of an assessment tool in remission and relapse phases. Similarly, because PGA is possibly insufficient as the standard for current activity, imaging is also necessary for longterm comparisons. However, routine imaging, without symptoms or signs of clinical activity, is currently not the usual practice in most experienced centers in Turkey.

ITAS2010 seems a practical assessment tool, taking only a few minutes in daily practice. Both ITAS2010 and ITAS-A had discriminatory value for active disease during the followup, but the agreement between PGA and ITAS2010/ITAS-A is observed to be moderate in our study. Future work on ITAS should include the incorporation of advanced vascular imaging, demonstration of the instrument's use as a meaningfully scalable measure and not simply a dichotomous measure of activity/flare versus remission, and validation of the tool in different cohorts by other investigators.

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