Abstract

Objectives. There are no valid instruments to measure disease activity in Takayasu arteritis (TA). We aim to provide a valid measure to assess clinical disease activity with or without incorporating acute phase reactants.

Methods. The Indian Takayasu Clinical Activity Score (ITAS) was initially derived from disease manifestations scored in the Disease Extent Index (DEI.Tak). The ITAS was validated by a group of physicians scoring both live and paper cases for inter-rater reliability (IRR), convergence with BVAS, correlation with the Physician’s Global Assessment (PGA) and ESR/CRP. It was further validated at a single centre in 177 patients for its ability to discriminate between active and inactive disease state at first visit and sensitivity to change in 132 active patients measured serially at two follow-up visits. ITAS-A also included graded scores for ESR/CRP.

Results. The final ITAS2010 contains 44 items with 33 features arising from the cardiovascular system. Seven key items are weighted to score 2 and all others score 1 only. Inter-observer variability was highly satisfactory (IRR 0.97). The ITAS showed superior inter-rater agreement compared with the BVAS (IRR 0.9) and PGA (IRR 0.82). In the single-centre study, median ITAS scores at first visit were significantly higher in active disease (5.62 ± 3.14) compared with grumbling (3.36 ± 1.96) and inactive disease (1.27 ± 1.26, P < 0.0001). The therapy induced a significant decrease in the ITAS2010 but the higher ITAS-A scores remained elevated.

Conclusion. The ITAS2010, validated in over 300 TA patients and sensitive to change, is a useful measure of clinical disease activity for patient monitoring. Higher ITAS-A scores suggest poor control of active disease by current therapy.

Key words: Takayasu arteritis, activity index, India, IRAVAS, large vessel disease, longitudinal studies, acute phase response.

Introduction

Takayasu aortoarteritis is a rare form of large vessel vasculitis (LVV), more common in Asia, which presents with acute vascular occlusion or hypertension in younger age groups. There is no validated clinical instrument to quantify disease activity in Takayasu arteritis (TA) for treatment decisions. The currently used NIH criteria [1] categorizes patients as active in the presence of certain limited features along with elevated inflammation markers. The clinical criteria are neither validated nor quantitative, while acute phase response may not parallel vessel wall inflammation in LVV. In small vessel vasculitis (SVV), validated
tools such as the BVAS, Vasculitis Damage Index (VDI) and Disease Extent Index (DEI) have been developed to assess disease activity, damage and extent [2–6]. The BVAS has proved its value as a clinical assessment of disease activity in SSV [7] and a recent update has included minor adjustments informed by extensive experience [8]. The BVAS at presentation provides prognostic value, correlating with long-term mortality [9]. Accumulating scars as chronic disease progresses do not respond to the drugs for active vasculitis and require a separate approach, captured in the VDI [3, 10].

TA presents a distinctly different pattern to SSV. Current treatment decisions are based on a compound physicians' judgement, taking into account clinical status, acute phase response and imaging data. To replace the physicians' opinion with an evidence base, quantitative outcome assessments are needed that are specifically relevant to LVV. OMERACT has noted the particular challenge of developing these for TA [11]. The vasculitis special interest group of the Indian Rheumatology Association (IRAVAS) approached this challenge based on the plentiful case material available. TA is seen relatively commonly by Indian physicians and IRAVAS had previously validated the BVAS and VDI in India [12]. We used this experience to devise a clinical index of disease extent in TA, validated by analysis of 143 patients seen in two centres [13]. The resultant DEI.Tak was used by the Turkish group to assess disease activity [14], although it was designed to record disease extent including both activity and damage. Here we present data on the development and initial validation of a specific disease activity index. The Indian Takayasu Activity Score (ITAS2010) provides the first quantitative score of new active disease. We have further combined this with the acute phase response (either ESR or CRP) in the ITAS-A to examine whether this provides more comprehensive assessment of disease status. This is an essential first step toward a compound activity index and should prove useful for studies of treatment response in TA.

Patients and methods

Derivation

An IRAVAS expert group experienced in TA used a three-step approach. Initially the DEI was designed on the BVAS template using specific TA features. The DEI.Tak containing 71 items was used in the second step to collect data on 143 TA patients from two collaborating centres [13]. Subsequently this DEI.Tak database was used to select features that had occurred within a 3-month period, reflecting new vasculitic activity. These were assembled into a draft activity index [Indian Takayasu Activity Score (ITAS)]. Face value was assessed through usage by several clinicians, including cardiologists and neurologists as well as rheumatologists. The content value of the ITAS2010 was analysed by both paper and live cases in serial group workshops where case presentations covering a spectrum of disease severity and duration were prepared to provide two time points for assessment. Finally, one investigator (D.D.) collected ITAS2010 scores from 177 patients in a new clinic setting, including serial assessments of the response to therapy.

Weighting

Seven ITAS2010 items [five cardiovascular system (CVS) items together with stroke and hypertension] were selected by consensus as of major importance and a weighting of 2 was applied, while all other items scored 1—giving a theoretical maximum score of 51. The effect of this was examined in a random subgroup of 132 of the clinic patients to determine whether a simple or a weighted score provided better separation of the patients labelled active on Physician Global Assessment (PGA) from the rest.

The comprehensiveness was examined by the number of features entered in the other items box, after repeatedly stressing the need to record features not covered in the score sheet. The number of redundant items was derived from scrutiny of features scored in <5% of the large clinic series. These were removed so that the short final ITAS2010 form was easier to use in the clinic.

To examine convergent validity in the absence of a gold standard in TA, the ITAS2010 was compared with the BVAS, with the PGA scored on either an ordinate 3-point scale (active, grumbling/persistent disease or inactive) or a continuous scale from 0 to 10 and with the acute phase response (ESR or CRP). The reliability of the ITAS2010 was tested by inter-rater agreement using an intraclass correlation coefficient (ICC) for both single and average measures in group exercises for the PGA, BVAS, ITAS2010 and ITAS2010 cardiovascular subscore.

Response to change

Longitudinal data were collected at approximately 3-month intervals on three occasions in the clinic series. The response to new therapy was analysed for the majority (132 patients) presenting with active disease. Response to flare was analysed in cases relapsing after initial assessment in clinical remission.

Statistical analysis

Data were analysed using a standard SPSS version 16 software package. The correlation of the ITAS2010 with the BVAS was assessed by Pearson’s correlation coefficient. The inter-rater reliability was assessed using the ICC. The ICC can be interpreted as the proportion of the total variance attributable to the underlying true estimate. Statistical comparisons were done between active/grumbling vs inactive disease and between active and grumbling disease using Bonferroni’s correction.

Results

The final ITAS2010 form (see supplementary data, available at Rheumatology Online) contains 44 items in six organ-based systems. The CVS, the most important system in TA, has 33 items in the ITAS with emphasis on bruits, pulse loss and claudication. The presence of any one of four major cardiovascular features (e.g. pulse loss)
point the assessor to progress to scoring details of the site(s) involved. Pulse loss scores include evidence of blocked vessels documented in the vascular imaging that forms part of the standard assessment of patients presenting with new disease flares. Each feature present is given a score of 1, except for seven major features such as bruit, which are weighted to score 2. Disease-relevant features not on the form are documented under other items. ESR/CRP and PGA are also recorded. A glossary is available to standardize application (see supplementary glossary, available at Rheumatology Online). Only new items (occurring during the previous 3 months) are scored at follow-up. However, at the first assessment of active patients, all positive items are scored unless documented as present at a previous medical examination, because patients are often unaware of the duration.

The clinical utility of the ITAS2010 was shown by application to a large single-centre series. The ITAS2010 (5.6 ± 3.13) in 132 patients clinically active by PGA was significantly higher than in 33 patients with inactive disease (1.27 ± 1.26, \( P < 0.001 \)) and 11 patients with grumbling disease (3.36 ± 1.96, \( P < 0.05 \)). The ITAS2010 in grumbling disease was still significantly higher than in inactive disease (\( P < 0.001 \)).

The CVS component of the score was re-evaluated separately in 130 patients at first assessment. This CVS subscore ranged from 1 to 16. The majority of patients (65%) had only one to five items present and their mean ITAS2010 score was 5. Here, the CVS component contributed at least two-thirds of the total ITAS. Similar proportions were seen for the smaller group with a high CVS component score, which ranged from 6 to 16. Weighting of the major CVS items gave a clearer separation of patients graded active on the PGA from the grumbling and inactive groups examined separately or together and was adopted as the standard for the ITAS2010.

The comprehensiveness of the ITAS2010 was examined in a cross-sectional study. CVS involvement was recorded in 131 of 132 patients with active disease. Outside the CVS, only renal (31%) and CNS (21%) systems were scored frequently (Fig. 1). Minor systemic items were scored in 45% of patients—most commonly myalgia/arthralgia, headache and malaise, but fever occurred in only 4%. Within the CVS, new pulse loss was noted in 51% (Fig. 2). The arm was the most common site (brachial in 48%, radial in 54%), but pulse loss threatening limb viability was rare (in two cases only). The carotid pulse was absent in one-third of cases and femoral, popliteal and foot pulses were absent in one-quarter (Fig. 3). Bruits were most commonly noted in the carotids (37%), where the frequency was very similar to that of pulse loss at that site. The subclavian artery (24%) was the only other common site for bruits. Pulse inequality was almost universal. Claudication was frequent (78%), but congestive heart failure was uncommon (10%).

Reliability
The reproducibility of the new score was tested in several ways. Inter-observer variability assessed using eight live patients and five paper cases at a group workshop was highly satisfactory. The ITAS2010 showed superior inter-rater agreement, average ICC and Cronbach’s alpha (average value 0.97; CI 0.95, 0.99) than the BVAS (average score 0.90; CI 0.72, 0.98) and PGA (average score 0.82; CI 0.63, 0.94), although both were statistically significant (\( P < 0.001 \)), indicating that the ITAS2010 is a reliable measure of disease activity in TA and appears superior to the BVAS or PGA, as the confidence intervals for the latter were markedly wider. The inter-rater variability was also calculated separately for the important CVS component of the ITAS2010 assessment. The single measure and average measure for the CVS component of the ITAS2010 were 0.857 (CI 0.741, 0.944) and 0.984 (CI 0.966, 0.994), respectively, both being statistically significant (\( P < 0.001 \)).

Convergent validity
The convergent validity was further examined in the single-clinic series by comparing the ITAS2010 with both...
the PGA commonly used in clinical assessment of aortoarteritis and the well-validated BVAS index. The ITAS2010 score showed a good correlation with the PGA (correlation coefficient \( r = 0.512, 0.642, 0.726 \) for first, second and third assessments, respectively, \( P < 0.001 \) for all visits) and BVAS (\( r = 0.749, 0.548 \) and 0.693; \( P < 0.001 \) for all visits). In the group exercise the ITAS2010 again correlated with the PGA scored on a 10-mm analogue scale across the range (\( r = 0.502, P < 0.05 \)). There was also a significant correlation with the BVAS (\( r = 0.578, P < 0.05 \)). Total ITAS scores were higher than the BVAS on 149 of 201 occasions, suggesting that the former is a more sensitive assessment tool for this disease.

The convergent validity was further examined using the acute phase response in the clinic series. The ESR showed a weak correlation with ITAS2010 scores (\( r = 0.218, P < 0.01 \)) but not with CRP (\( r = 0.177, P < 0.12 \)). No significant association of elevated ESR/CRP was noted with either systemic disease or the CVS subsection.

**Value of incorporating acute phase response**

The ESR or CRP is considered an important aspect contributing to the PGA, particularly when considering the need for therapy. Here we examined the effect of adding a graded acute phase to the clinical score. An ESR was available in 88 patients. The ITAS + ESR score was significantly (\( P < 0.001 \)) higher in 66 patients with active disease (6.9 ± 3.67) than 20 patients with inactive disease (2.2 ± 2.07), but not in 5 patients with grumbling disease (5.0 ± 3.32). Even though the mean ITAS + ESR score was higher in grumbling disease than inactive disease, this failed to achieve statistical significance. Likewise, the ITAS + CRP score was significantly (\( P = 0.001 \)) higher in 39 patients with active disease than 7 patients with inactive disease. The effect of combining patients graded on the PGA as active or grumbling gave a single active group of 143 patients to compare with the 33 inactive cases (Fig. 4). In 68 and 44 patients, respectively, ITAS + ESR (6.57 ± 3.59) and ITAS + CRP (6.57 ± 3.55) were significantly elevated (\( P < 0.001, P = 0.001 \)) compared with 20 (2.2 ± 2.0) and 7 (2.14 ± 1.32) patients, respectively, with inactive disease.

There is a wide scatter of values included in this overall active group. We suggest a cut-off point of 4 for the ITAS-A to differentiate active and inactive patients, based on the mean ± 2 s.d. of these groups (supplementary Tables 1 and 2, available at Rheumatology Online). Thus an ITAS-A of 5 or greater indicates disease activity. This contrasts with a score of 2 or more on the ITAS2010.

**Response to change**

Responsiveness to change was examined by serial ITAS2010 and ITAS-A scoring in the large clinic series. New active therapy induced a significant decrease in the weighted score of 85 active patients reassessed after clinical improvement (Fig. 4A). The close correspondence between ITAS-A derived from either acute phase marker (Fig. 4A) justified using the two interchangeably in the ITAS-A. The degree of change was most marked between assessments 1 and 2 during the first few months of therapy. However, the value of the ITAS-A remains elevated at the third assessment, after at least 6 months of therapy. The significance of this requires further investigations. Serial assessments in six individuals with inactive disease at first assessment who later relapsed (Fig. 4B) showed that ITAS2010 and ITAS-A captured disease activity in these flares although the scores were lower in relapse than at first presentation with active disease. This may relate to the shorter duration of active disease in a relapse associated with early presentation of patients educated to return to the clinic with any fresh symptoms.

**Discussion**

The OMERACT group suggested that clinical assessment of disease activity is essential in TA [11]. This study presents the first validation of both a clinical assessment instrument, the ITAS2010, and a composite ITAS-A including clinical plus acute phase reactants specifically developed to score disease activity in TA. The derivation of the ITAS2010 items was data driven, assisted by prior experience with activity scores in SVV [12]. The three-step process involved patient series from three major centres and group case discussions in six others. The ITAS2010 was derived from the DEI.Tak, but excluding features that
Assessing disease activity in TA is difficult in the absence of a gold standard. The PGA is based on clinical features, acute phase reactants and image abnormalities. Systemic manifestations are easy to monitor in TA, but vascular imaging may reflect activity or damage. The ITAS2010 is a comprehensive clinical assessment that captures recent manifestations with the potential to reverse. The acute phase response is neither sensitive nor specific enough to be helpful if used alone. ESR/CRP is not necessarily elevated, even in acute vascular occlusions, and in our large series ESR showed only weak correlations with the ITAS2010. However, as ESR/CRP is widely used in making therapeutic decisions, the ITAS-A incorporating graded ESR or CRP values was also calculated. The performance of the ITAS-A was comparable to that of the ITAS2010, but values were higher and remained elevated even after clinical response to induction therapy.

Previous clinical scores for TA, such as the NIH criteria, focused on a few major items. In this respect, the ITAS2010 is comparable to the BVAS, which is widely accepted to detail the extent of activity in SVV. The ITAS2010 contains fewer organ-based systems and fewer individual items than even the recent slimmed down BVAS3, but inclusivity has been preserved. The ITAS2010 contains the key features, including scalability, favoured by the Turkish expert group to determine disease activity. The central importance of CVS involvement in aortoarteritis was confirmed by positive CVS scores in clinically active patients. The frequency of bruit, pulse inequality, new pulse loss and claudication informed the consensus to weight these important features, together with stroke and renal hypertension. Weighting helps to counteract the problem of low scores despite active disease in patients with pulse loss in a single vessel. Here it was able to distinguish cases active by the PGA from the combined grumbling and inactive cases.

The time limit for inclusion of events in the ITAS2010 was set at 3 months. The progression of TA is much slower than that of ANCA-associated vasculitis, confirmed by changes in MRI or PET following therapy. The clinical utility of the ITAS2010 was shown by its reproducibility and sensitivity to change. It is essential for an activity score to document response to therapy. The decrease in ITAS2010 scores after presentation may be influenced by reversion to the mean, but the response to flare is clearly not. The ITAS2010 provides an activity index usable in clinical situations where repeated assessments are needed or costs limit the use of imaging. The PGA, the usual approach to current therapy decisions, showed reasonable inter-observer correlations in the single centre where the team worked closely together, but lower correlations were seen in the group exercise. In the wider world, clinicians do not always agree on the severity of disease activity.

A standard assessment like the ITAS2010 helps inexperienced clinicians to collect a relevant data set for informed therapeutic decisions. In real life these decisions also take account of data from vascular imaging and acute phase responses. Standard vascular imaging shows damage as well as activity and may not reverse with medical therapy. The CVS component of the ITAS2010 takes some account of image abnormalities, particularly evidence of vessel occlusion. If this fits with the clinical picture of a new event, it forms part of the scoring of the ITAS2010, even though it could be argued that it actually represents damage, a scar of past disease. The role of vessel narrowing in assessment is more difficult, and we are currently examining the utility of a complex database to combine several aspects of luminal changes in a quantitative score. Imaging for vessel wall inflammation is improving, but neither PET nor MRI changes correlate closely with clinical lesions.

PET scanning has real potential to document inflammation, but at present it is far from clear what pathology it represents. Hot scans may represent active lesions but do not return rapidly to normal after therapy-induced clinical remission and thus may be metabolically active healing lesions. Biopsy data are scanty while serial angiographic studies show fresh lesions occurring in two-thirds...
of patients even in clinical remission [1]. Our preliminary study has not shown a simple correlation of PET scans with clinical changes scored on the ITAS2010 (R. Salmond, unpublished results) and more work is required.

There remains considerable discussion about the lack of correlation of acute phase response measures with other data in TA [15–17], but their standardized assays are easier to incorporate into clinical scores, as we have done in the ITAS-A. The graded ESR and CRP values selected showed close correlations, allowing us to group them together in the ITAS-A. The data derived from this exercise pose new questions to be answered by further experience. The values of the ITAS-A after 6 months of active therapy suggest continuing low-grade activity, consistent with evidence of continued activity in biopsies [19] and a high relapse rate when steroids are withdrawn [19]. However, there is a danger that the raised ITAS-A values, which can persist even for 1 year after an apparent response to therapy, could confuse clinicians. Future work will investigate whether these raised values correlate with persistent vessel wall hot spots in PET scans [26]. Long-term follow-up is urgently needed to determine the possible clinical relevance of persistently raised ITAS-A. This may reflect the inadequacy of current therapies (derived largely from experience in SVV) or simply the slow response of the different pathologies in LTV. We have described a comprehensive yet concise instrument to measure clinical disease activity in TA for such studies. The strength of the ITAS2010 and ITAS-A is the derivation mainly from radiological or biologic features [32]. The recent French report on infliximab in TA also noted the difficulties in assessing disease activity and therefore evaluated clinical response separately from radiological or biologic features [32]. The ITAS2010 includes all the clinical features selected in a standardized validated format. Thus it provides a more reproducible assessment of disease severity than the PGA.

This study has several limitations, and like the BVAS and BILAG [8, 28], the ITAS2010 will doubtless need to be modified with experience in wider patient populations. The ITAS2010 will have little use in scoring activity before major vessel involvement leads to focal manifestations, but presentation with preocclusive arterial disease is very uncommon in India and Japan [18]. MRI and PET vessel wall images have been proposed to diagnose early disease [29]—particularly in the rare cases presenting as pyrexia of unknown origin [30, 31]. However, in established disease it is not clear whether hot PET scans represent active inflammation or healing [20]. The recent French report on infliximab in TA also noted the difficulties in assessing disease activity and therefore evaluated clinical response separately from radiological or biologic features [32]. The ITAS2010 includes all the clinical features selected in a standardized validated format. Thus it provides the first quantitative clinical score on which to base the future development of a compound index.

In summary, the ITAS2010 and ITAS-A will have immediate usefulness in standardizing clinical assessment of response to therapy, with particular impact in developing countries where cost limits repetitive imaging in usual practice. The sensitivity to change demonstrated here and recently confirmed in a trial of tocilizumab therapy [33] shows that the ITAS2010 is a suitable clinical tool to quantify response. Thus it can make an important contribution to the randomized clinical trials so badly needed to provide TA with an evidence base for therapy.

Rheumatology key messages

- Standardized validated assessments are needed to quantify the severity of disease activity in TA.
- The new ITAS2010 is sensitive to treatment.
- The ITAS-A is a composite disease activity index using both clinical and acute phase parameters.

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Supplementary data

Supplementary data are available at Rheumatology Online.

References


