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Concise report

Assessment of disease activity and progression in Takayasu's arteritis with Disease Extent Index-Takayasu

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Abstract

Objective. Disease Extent Index-Takayasu (DEI.Tak) is a new index developed for the follow-up of Takayasu's arteritis (TA), assessing only clinical findings without the requirement of imaging. We investigated the effectiveness of DEI.Tak in assessing disease activity and progression by comparing with physician's global assessment (PGA) and active disease criteria defined by Kerr *et al.*

Methods. The initial DEI.Tak forms were filled in for 145 TA patients cross-sectionally to detect the baseline damage and after 29.8 (31) months ($n = 105$, 144 visits) only by including the new/worsening symptoms within the past 6 months.

Results. At baseline, all patients had a DEI.Tak >0 [mean (S.D.): 7.6 (4.2)]. At this evaluation, 62% of the patients had active, 16.2% had persistent and 21.8% had inactive disease according to the PGA. At follow-up, in 69% of the patients the DEI.Tak score was 0. However, 14% of them were accepted as having active and 17% persistent disease according to PGA. In contrast, 18% with a DEI.Tak $\geqslant 1$ were inactive according to PGA. Patients with active or persistent disease with PGA had higher DEI.Tak compared with inactives [1.3 (1.9), 1 (1.3) *vs* 0.2 (0.6), respectively; $P < 0.001$]. According to Kerr's criteria 27% were active. The total agreement between DEI.Tak and Kerr's criteria was 94% ($\kappa = 0.85$). Compared with PGA, Kerr's criteria had a total agreement of 74% and DEI.Tak 68%.

Conclusion. During follow-up, most TA patients showed no clinical activity with DEI-Tak. Although the agreement between Kerr's criteria and DEI.Tak seemed very good, using Kerr's criteria instead of DEI.Tak increased the consistency with PGA, which could be explained by the influence of imaging data and acute-phase reactant levels on the physician's decisions.

Key words: Takayasu arteritis, Disease activity, DEI.Tak, Birmingham vasculitis activity score.

Introduction

Takayasu's arteritis (TA) is a large-vessel arteritis, mainly affecting the aorta, its major branches and the pulmonary artery. The incidence is ~2.6 cases per million per year but may increase up to 1 in 3000 cases, as reported in an autopsy series from Japan [1–3]. The low prevalence of the disease makes it difficult to provide a standardized approach for diagnosis, treatment and follow-up of TA. Angiography has been the gold standard for the diagnosis, but efforts continue to replace it with other imaging modalities such as ultrasonography, magnetic resonance (MR) angiography and PET imaging [4].

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CLINICAL SCIENCE

Assessment of disease activity in TA is challenging. Most of the systemic manifestations are not specific to vasculitis, and vascular features progress very slowly [5]. Clinical features do not correlate with acute-phase reactants in half of the TA patients [6–10]. In contrast to other vasculitides that affect the small- and medium-sized vessels, histology is rarely available to diagnose and assess activity of TA patients. Imaging modalities may highlight an active disease if a baseline imaging modality is performed at the first evaluation; however, due to cost, technical difficulties and side effects of the contrast agents, they are harder to use in routine follow-up. MR angiography and PET, observed to be promising in disease diagnosis, seem to be unreliable for follow-up, as nearly half of the patients in clinical remission have contrast uptake in follow-up imaging [11, 12].

Disease Extent Index-Takayasu (DEI.Tak) [13] is a new index developed for the follow-up of TA, assessing only clinical findings without the requirement for imaging techniques [see supplementary data, DEI.Tak Index, available at *Rheumatology* Online. The DEI.Tak Index has been published with permission from the Indian Rheumatology Association Vasculitis study group (IRAVAS)]. We investigated the effectiveness of DEI.Tak for evaluating current disease activity and recent disease progression by comparing it with physician's global assessment (PGA) and active disease definition of Kerr *et al*. [8].

Patients and methods

Patients

One hundred and forty-five TA patients meeting the ACR criteria for TA from eight centres were enrolled [14]. As the DEI.Tak form has been available since 2006 the forms were filled retrospectively for patients who were in routine follow-up until 2006 and new cases between 2006 and 2009 were prospectively enrolled. Informed consent was obtained from all patients participating in the TA registry. The study was approved by the local ethics committee of Marmara University Medical School.

Disease activity assessment

The initial DEI.Tak forms were filled cross-sectionally for 145 TA patients to detect the baseline damage, independent of the duration of symptoms. Follow-up using the same index was performed in 105 patients (144 visits) at intervals of at least 6 months only by including new or worsening symptoms within the past 6 months, to reflect current activity. In addition to DEI.Tak, which only uses the clinical findings and physical examination, acute-phase reactants, progress in imaging modalities (whenever available) and therapy decisions were recorded. Patients were also categorized for having active disease according to a modified Kerr's criteria [8], which defines 'active disease' if two of the following are positive: (i) systemic features with no other cause; (ii) elevated ESR; (iii) features of vascular ischaemia or inflammation (claudication, diminished or absent pulses, bruit, vascular pain, asymmetric blood pressure; and (iv) typical angiographic features (including any imaging method in addition to conventional angiography). DEI.Tak scores were compared with PGA, acute-phase response, treatment changes and activity according to the Kerr criteria.

Statistical analysis

Continuous variables were expressed as median (range) according to the variability of distribution. Kruskal–Wallis test was employed to assess the differences in DEI.Tak scores between different PGAs and therapy decision groups, followed by evaluation with the Mann–Whitney U-test for multiple comparisons. Resulting *P*-values were corrected according to the Bonferroni method. The agreement between DEI.Tak and Kerr's criteria was estimated by using κ statistics (unweighted κ for dichotomous assessment). The percentage of exact agreement was calculated for DEI.Tak, Kerr's criteria and PGA. Correlation of ESR and DEI.Tak was analysed by Pearson's correlation test. Statistical analysis was performed with the package MedCalc software (v.9.2 for Windows).

Results

Baseline evaluation

Seventy-eight per cent of TA patients were female. Median (range) age was 38 (13, 73) and the disease duration was 8 (1, 37) years. Age at disease onset was 28 (6, 64) years. Patients had a median 1 (0, 31) years of delay in diagnosis. Fifty-eight per cent of the patients were under immunosuppressive medication. In addition to steroids, 46 patients were on MTX, 18 patients AZA, 4 patients cyclophosphamide, 1 patient mycophenolate mofetil, 1 patient TNF-antagonist therapy and 1 patient LEF. Eight patients were using only steroids and five patients were using MTX or AZA without steroids. Twenty-nine patients had had prior vascular surgery and 19 had had percutaneous angioplasty.

At the initial assessment, all patients had a score >0, with a mean initial DEI.Tak score of 7.6 (4.2). At this evaluation, 62% of patients had active, 16.2% had persistent and 21.8% had inactive disease according to PGA. The positive findings according to DEI.Tak are listed in Table 1.

Follow-up evaluation

The mean time period between the first and final evaluations was 27 (29) months. The demographic variables of patients who had follow-up evaluations were similar to those of the whole group. The positive findings according to DEI.Tak are listed in Table 1.

Most of the second evaluations [100/144 (69%)] showed no difference according to DEI.Tak (score = 0). However, 14% of these patients ($n = 14$) were accepted as having active and 17% ($n = 17$) persistent disease according to PGA (Table 2). On the other hand, 18% of patients (8/44) with a DEI.Tak $\geqslant 1$ were inactive according to the PGA (DEI.Tak related to systemic symptoms in three, renal manifestations in three, new bruits in one, pulse loss in two and eye manifestations in one patient—with some

Table 1 The baseline and follow-up assessments of DEI.Tak

Manifestations	Baseline (145 patients)	Follow-up (105 patients/ 144 visits)
Systemic	79 (55)	18 (13)
Cutaneous	6 (4)	2 (1)
Mucous membranes	0 (0)	0 (0)
Eyes	15 (10)	5 (4)
Ear–nose–throat	2 (1)	1 (1)
Chest	27 (19)	2 (1)
Abdomen	10 (7)	2 (1)
Renal	49 (34)	10
Central nervous system	15 (10)	0 (0)
Genitourinary system	5 (3)	0 (0)
Cardiovascular system		
Bruits	99 (69)	6 (4)
Pulse and BP inequality	47 (32)	2 (1)
Pulse loss	105 (72)	8 (6)
Claudication	71 (49)	6 (4)
Other cardiac findings	27 (19)	7 (5)
Other vascular items	4 (3)	0 (0)
ESR, median (range), mm/h	30.5 (1, 139)	18 (0, 90)
ESR > 20 mm/h	86 (65)[a]	60 (44)[b]
CRP, median (range), mg/l	6.7 (0, 162)	3 (0, 87)
CRP > 5 mg/l	72 (55)[a]	41 (31)[a]
DEI.Tak; median (range)	7 (1, 22)	0 (0, 6)

Values represented as *n* (%) of patients unless otherwise mentioned. [a]Available in 132 patients. [b]Available in 136 patients.

Table 2 DEI.Tak and Kerr's criteria compared with PGA according to disease activity in TA patients

Activity by indices		PGA		
		Inactive	Persistent	Active
DEI.Tak	0	68	17	14
	>0	8	24	12
Kerr's criteria	Inactive	64	15	8
	Active	3	19	10

Values are represented as number of assessments.

patients having more than one finding). According to PGA, patients with active or persistent disease had higher DEI.Tak compared with inactives [1.1 (1.7), 1.2 (1.4) *vs* 0.2 (0.6), respectively; $P < 0.003$]. A weak correlation between ESR and follow-up DEI.Tak scores was observed ($r = 0.17$; $P = 0.05$).

Drug modification data could be obtained in 101 assessments. Therapies were kept the same in 68 patients, 15 patients had the same therapy with higher doses, 16 patients had new immunosuppressive treatments and drugs were tapered down in 2 patients. Patients requiring an increase in drug dose or new therapies also had higher DEI.Tak scores compared with patients without modification [1.4 (1.5), 1.7 (1.9) *vs* 0.4 (0.7), respectively; $P < 0.003$).

Kerr's criteria using imaging modalities could be applied in 119 evaluations. According to Kerr's criteria, 32/119 patients were active (27%) (Table 2). The total agreement between DEI.Tak and Kerr's criteria was 94% ($\kappa = 0.85$). Compared with PGA, Kerr's criteria had a total agreement of 74% (88/119) and DEI.Tak 68% (97/144). Nine of 19 patients (47%) who had a progression according to imaging findings had a DEI.Tak score of 0. Six of them had a therapy modification depending on imaging findings despite the absence of symptoms.

DEI.Tak in patients with new diagnosis

A subgroup of patients with new diagnosis were separately assessed ($n = 46$). The age and follow-up duration of this subgroup was similar to patients with established disease (data not given). Within these patients, 41 of them had a second DEI.Tak and Kerr's assessment. The agreement between two assessments and PGA were like the ones with established disease [the total agreement between DEI.Tak and Kerr's criteria: 95% (39/41). Compared with PGA, Kerr's criteria had a total agreement of 78% (32/41) and DEI.Tak 72% (33/46)].

Discussion

According to the OMERACT Vasculitis Study Group, a vasculitis disease activity tool should have the ability to quantify disease activity on a continuous scale over both short and long periods of time and distinguish between high, low disease activities and remission [15]. In this context, disease assessment in TA may depend on clinical assessment of constitutional symptoms, vascular signs, acute-phase response and vascular imaging, which are reflected in the most widely used tool, Kerr's criteria. Although some studies relied on only clinical features and acute-phase response [16] most studies preferred to use imaging also, although not validated sufficiently [4].

However, as imaging modalities are difficult to use in routine follow-up and acute-phase response is not uniformly observed, DEI.Tak is prepared aiming to assess disease severity and extension mainly with clinical features. Only new or worsening of symptoms are supposed to be involved with one point for each symptom. One major disadvantage is about the uncertainty of the timing of physical examination findings. Although the questionnaire refers to 'new or worsening symptoms within the last six months', it is impossible to decide the timing of a murmur or a pulse loss if the patient is evaluated for the first time and again quite difficult in the follow-up due to insufficient quantification of a murmur. In this context, DEI.Tak in the first visit, especially in long-standing disease, seems to serve as a 'damage index' showing the extent of past and current vascular involvement that is usually irreversible.

The first part of DEI.Tak is mostly about the clinical history related to organ involvement in TA. A few other parameters such as hypertension and renal insufficiency (with serum creatinine and urine protein levels) are also

evaluated. The advantage of this detailed questionnaire is that no major organ involvement can be missed. Items were recorded in the 'Other vascular items' box only in four patients (3%) demonstrating the extensive coverage of DEI.Tak. However, some questions such as those related to mucous membranes were never marked as 'present' in our cohort. In addition, questions about ear–nose–throat, skin and genitourinary system were marked in <5% of patients both initially and at follow-up, which raises doubts about the relationship between these symptoms and the disease. The high number of questions increases the sensitivity of the index at the cost of losing specificity and time. One of the other disadvantages compared with the Birmingham vasculitis activity score, the validated tool for small- and medium-vessel vasculitis, is the unweighted appraisal of the symptoms. 'Arthralgia' counts the same weight as 'sudden vision loss' does; however, a patient having the latter should be regarded as a severe case despite having the same DEI.Tak score as the former one.

The second part of DEI.Tak includes a detailed evaluation of the cardiovascular system. A history including claudication of the extremities and carotidinia as well as physical examination findings such as pulse loss and murmurs are involved in this part of the index. Although both new and worsening symptoms are included in the index, as it is practically not possible to realize worsening of a murmur in a 6-month interval, we think physical examination findings in DEI.Tak are only helpful when there is narrowing or occlusion of a new vessel that was not involved before. An imaging method is usually required to detect the worsening of an already narrowed vessel.

Acute-phase response is influenced by many variables including hypergammaglobulinaemia, recent infections or age. Accordingly, in half of TA patients' acute-phase reactants do not correlate with the disease activity [6–10]. Despite this literature, however, in our cohort, ESR and CRP levels were also used as major indicators of disease activity by most of the rheumatologists and it is possibly a major cause of discordance between DEI.Tak and PGA as well as therapy decisions. As physicians seem to take into account acute-phase reactants as valuable information for disease activity assessment, the inclusion of these laboratory findings would increase the consistency of DEI.Tak.

Excluding the imaging modalities in DEI.Tak also causes a significant loss of information about the extension and activity of the disease process in TA. In a subgroup of our cohort (depending on centres' individual approaches), patients had routine MR angiography or Doppler ultrasonography, regardless of their symptoms. The worsening of findings in either imaging method was possibly the other cause of discordance between DEI.Tak and PGA. Although, DEI.Tak aims to assess TA without imaging, we think including a progression in any imaging modality will improve the consistency of DEI.Tak with PGA.

One of our limitations is the duration of the follow-up. TA is a relatively slow progressive disease that usually responds quickly to initial immunosuppressive therapy [16]. In the current study, 62% of patients had active disease at the initial assessment, mostly diagnosed as having TA and immunosuppressive therapy was started for the first time. The high percentage of patients with inactive disease at the follow-up decreased the power of the study. Longer duration of follow-up will provide more information about the capacity of DEI.Tak to assess activity in TA.

In conclusion, DEI.Tak seemed to be a practical, valuable tool to assess disease activity and progression in TA. However, in a significant subset of the patients, the presence of active or persistent disease was determined by the physician using other outcome parameters. Although the agreement between Kerr's criteria and DEI.Tak appeared to be very good, using Kerr's criteria instead of DEI.Tak increased the consistency with PGA, which could be explained by the influence of imaging methods or acute-phase reactants on physician's decisions. Therefore, we think that acute-phase response and a progression in any imaging modality should be incorporated into a modified DEI.Tak.

Rheumatology key messages

- DEI.Tak, an index with only clinical findings, may be helpful to evaluate TA.
- PGA has a good consistency with DEI.Tak and slightly better with Kerr's criteria.
- Our observations suggest that imaging and acute-phase response also influence management decisions.

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Supplementary data

Supplementary data are available at *Rheumatology* Online. The supplementary data has been published with permission from the IRAVAS (the Indian Rheumatology Association Vasculitis study group).

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