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Editorial

Disease assessment in Takayasu's arteritis

How useful is ITAS2010 for the researcher and the clinician?

EDITORIAL

This editorial refers to Development and initial validation of the Indian Takayasu Clinical Activity Score (ITAS2010), by Ramnath Misra *et al*., on pages 1795–1801.

Takayasu's arteritis (TAK) is a granulomatous large-vessel vasculitis (LVV) affecting the aorta and its main branches, predominantly occurring in females with the diagnosis usually made in the second or third decade of life [1]. Disease assessment in TAK requires the evaluation of both constitutional and vascular features. However, despite the many cohort studies that have been published, there are no validated, quantitative outcome measures for TAK for use in clinical trials [2, 3]. Multiple empirical definitions of remission/relapse or activity defined by vascular imaging have been proposed. The most commonly adopted approach is the simple definition of active disease originally used in a study from the US National Institutes of Health (NIH) as the presence of constitutional symptoms, new bruits, elevated acute-phase reactants (APRs) or new angiographic features [4]. The lack of a gold standard for establishing disease activity in TAK presents a major challenge in creating useful and valid outcome tools for disease assessment.

The Indian Takayasu Clinical Activity Score (ITAS2010), presented in an article by Misra *et al*. in this issue of *Rheumatology* [5], is the latest attempt to develop a disease activity score for TAK. During the development stage of the ITAS, the disease-extent index (DEI.Tak), with 71 items, was created using the BVAS as a template. This was a reasonable approach since the BVAS is an established disease activity score for vasculitis that has been successfully used in most therapeutic trials of ANCA-associated vasculitis in the past decade and was recently endorsed by OMERACT as a validated measure for ANCA-associated vasculitis [6]. However, an important difference between the BVAS and ITAS2010 is that the BVAS incorporates nearly all of the disease features that clinicians routinely use to evaluate disease activity, such as disease manifestations, symptoms, physical examination findings, laboratory test results, and diagnostic imaging. In contrast, the ITAS2010 only evaluates the clinical features of the disease *newly* present in the prior 3 months assessed by the physician (except evidence of blocked vessels documented by vascular imaging for determining pulse losses). Items found to be rarely present (<5%) were deleted and a weighting system was applied to items of cardiovascular disease such as bruits, pulse inequality and hypertension. The ITAS2010 in its final form appears to be fairly easy to complete.

The ITAS2010 seems to have good comprehensiveness and the inter-rater agreement is better than the physician's global assessment (PGA) (0.97 *vs* 0.82) [5]. However, convergent validity, when assessed by comparison with the PGA, is quite low at the initial evaluation but improves at subsequent study visits ($r = 0.51$, 0.64 and 0.72) [5]. Although CRP and ESR had weak correlations with the ITAS2010, the authors made a further attempt to incorporate APRs into the score (ITAS2010-A) by adding an extra 1–3 points for elevated ESR or CRP. This change resulted in higher ITAS2010-A scores both in active and inactive patients [5]. Furthermore, when response to change was assessed by the ITAS2010-A, patients still had a mean score of 4 at the third visit, when they were deemed to be clinically inactive per the PGA [5]. That items on the ITAS2010 are still present even during apparent remission is problematic and illustrates the substantial difficulty in differentiating activity from damage due to non-vasculitis-related problems in this disease. The suggestion to have a cut-off of 4 points to separate active and inactive disease states does not satisfactorily address the underlying limitation to the ITAS2010 assessment method.

Physical examination for new vascular signs is a simple, first step for disease assessment in TAK and was chosen by the study investigators as the major tool in the ITAS2010. However, the limitations of physical examination were recently shown in a study comparing physical signs with imaging data [7]. Individual physical examination findings had poor sensitivity (14–50%), and even when used in combination, at least 30% of arteriographic lesions were missed. Clinical assessment therefore only partially reflects the physicians' decision process, and elevated APRs and new findings in imaging studies are usually accepted to be indicative of ongoing, active disease in TAK. The low correlation of the ITAS2010 with the PGA suggests that some physicians might accept as active only patients with increased APRs or new abnormalities on vascular imaging studies. Imaging methods such as computerized tomography (CT) and magnetic resonance (MR) angiography show lumenal changes with increasingly better definition. The clinical utility of CT or MRI for determining vessel wall enhancement or thickening remains controversial. Serial changes in perceived wall physiology are considered by some investigators to be indicative of active disease, but the necessity of directing treatment based on CT or MRI findings is unproven. PET, often combined with CT, is also gaining acceptance as a diagnostic tool, with similar concerns about this

modality's use for assessing disease activity. Ongoing research into the uses of CT, MRI, and PET in LVV will help define their roles, including work on new contrast agents that may be more specific for vascular inflammation and help differentiate the effects of vasculitis from the impact of atherosclerosis.

In a study of the DEI.Tak by the Turkish Takayasu Study Group, patients with active or persistent disease had higher DEI.Tak scores compared with inactive cases; however, similar to the current study of the ITAS2010, the PGA and DEI.Tak had only modest agreement (68%) regarding disease state [8]. Furthermore, among the DEI.Tak-negative group, 31% were felt to have active disease per PGA, while 18% of patients with a DEI.Tak score $\geqslant 1$ were considered inactive by PGA, possibly reflecting the influence of increased APRs or new imaging findings in the scoring of the PGA. It is not stated in the article by Misra *et al*. [5] to what extent a similar discordance between the ITAS2010 and PGA exists.

As outlined by the OMERACT Vasculitis Working Group, there is a clear need for developing a validated set of outcome measures for LVV for use in clinical trials and also in clinical practice [3]. A Delphi exercise for the assessment of disease activity in LVV is currently ongoing, with the ultimate goal of developing a core set of validated outcome measures that capture disease across the range of key domains of illness in TAK. The ITAS2010 seems to be a simple, reliable tool that might be helpful in disease assessment in TAK. However, additional studies of the ITAS2010 are required before it can be considered a standard tool for clinical research in TAK. The ITAS was fully developed and validated using data from Indian patients, therefore regional and ethnic differences leading to different phenotypes of disease extent and severity may influence its validity and generalizability when applied to different patient groups. Future work on this instrument should include the incorporation of APRs and advanced vascular imaging, further resolution of the issues surrounding activity *vs* damage, demonstration of the instrument's utility as a meaningfully scalable measure and not simply a dichotomous measure of activity/flare *vs* remission, validation of the tool in different cohorts by other investigators and, ideally, successful incorporation of the ITAS2010 into a therapeutic clinical trial. The work of developing and testing the ITAS2010 has been valuable in advancing the study of outcome assessment in TAK and helping to move the field closer to the goal of having a set of valid and feasible outcome tools for TAK for use in clinical research.

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