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Outcome measures for Takayasu's arteritis

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Abstract

Purpose of review—Takayasu's arteritis (TAK) is a large-vessel vasculitis with a chronic, indolent course affecting the aorta and its main branches. This review will describe the recent studies to develop validated outcome measures to assess TAK.

Recent findings—TAK is traditionally assessed with a physician's global assessment including symptoms and signs of inflammation and vascular insufficiency, acute-phase reactants (APRs), and imaging including conventional digital subtraction angiography, computerized tomographic, and magnetic resonance angiography, and recently 18-FDG-PET. Recent attempts to develop a validated tool for disease assessment include the Indian Takayasu Clinical Activity Score (ITAS2010), which incorporates clinical signs and symptoms with APRs in a simplified and weighted adoption of the Birmingham Vasculitis Activity Score. Among biomarkers to assess clinical activity, pentraxin-3 is perhaps the most promising, but its validity and superiority against APRs in clinical practice need to be demonstrated. Patient-reported outcomes (PROs) are increasingly recognized as of substantial importance to measure in clinical trials; in addition to so-called 'generic' tools such as the SF-36 or measures of fatigue, disease-specific instruments would likely help capture aspects of TAK not measured by generic quality-of-life assessments or physician-based tools.

Summary—Although outcome measures for TAK are not sufficiently validated, progress in the assessment of TAK is reflected in recent studies with new tools such as ITAS2010, new biomarkers, and a variety of PROs.

Keywords

disease assessment; outcome measures; Takayasu's arteritis

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Conflicts of interest

None.

INTRODUCTION

First described by Mikito Takayasu, a professor of ophthalmology at Kanazawa University, Japan in 1908 [1], Takayasu's arteritis (TAK) is a granulomatous, chronic large-vessel vasculitis (LVV) affecting the aorta and its main branches, occurring predominantly in females with the diagnosis usually made in the second or third decades of life [2,3■]. The most frequently involved vessels are the ascending and descending aorta, the subclavians, carotids, and vertebral arteries. Although the disease is observed worldwide, ethnic predispositions exist with most of the patients reported from East Asian countries including India, Japan, Korea, and also from Middle-Eastern countries such as Turkey. The disease generally has a prolonged, indolent course with constitutional features (fever, malaise, anorexia, and weight loss), extremity pain/claudication, and light-headedness. Bruits, absent or diminished pulses, and absence of measurable blood pressure can be present depending on the location and extent of vessel involvement [4]. Although prognosis in a recent Japanese series is reported to be improving [5], there is still a significant delay in the diagnosis and both morbidity and mortality are increased [6■,7■], with a high rate of new, severe manifestations after diagnosis [8■]. Vascular interventions are frequently performed to reestablish vascular patency; however, these procedures are associated with a high rate of re-stenosis or thrombosis [9■,10].

OUTCOME MEASURES FOR THE ASSESSMENT OF DISEASE ACTIVITY IN TAKAYASU'S ARTERITIS

As with all orphan diseases, the low incidence of TAK (approximately 0.004% in Japan [3■]) is a major limitation to conducting randomized controlled trials (RCT) and except for an ongoing RCT in North America (ClinicalTrials.gov Identifier: NCT00556439), there are no RCTs published in TAK [11■,12]. The treatment choices are mainly guided by observational studies and clinicians' decisions are largely based on expert opinion [13]. This is reflected in the recently published European League against Rheumatism (EULAR) guidelines for the management of LVV in which, except for a general recommendation for use of immunosuppressive agents, all recommendations for TAK are supported by low levels of evidence [14].

Another major reason for the lack of RCTs in the field of LVV is the absence of validated outcome measures. Although disease-related morbidity, treatment-associated toxicities, and mortality are usually reported in cohort studies and open-label clinical trials, research on outcome measures in TAK is quite limited.

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. Multiple empiric definitions of 'remission/relapse' or 'activity' defined by vascular imaging have been proposed [12]. A definition of 'relapse' with clinical and laboratory parameters is usually chosen and seems sufficient as the 'primary outcome' for an efficacy trial of a new intervention; however, several different aspects of disease assessment, such as patient-reported outcomes (PROs) or damage assessment, have not been sufficiently explored.

The most commonly adopted approach to disease assessment in TAK is the simple definition of ‘active disease’ originally used in a study [15] from the US National Institute of Health (NIH) as the presence of constitutional symptoms, new bruits, elevated APRs, or new angiographic features. A literature review determined that the items in the NIH series were preferred by most studies to define active disease [12].

The Birmingham Vasculitis Activity Score (BVAS) is a validated tool for small-vessel and medium-vessel vasculitis that records the evidence of active vasculitis including multiple manifestations of vasculitis, arranged by organ systems [16] and was also endorsed by Outcome measures in rheumatoid arthritis for clinical trials (OMERACT) for use in therapeutic trials of Anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (granulomatosis with polyangiitis and microscopic polyangiitis) [17]. In addition, several studies report BVAS as the main assessment tool for TAK, such as for comparing BVAS to 18-FDG-PET studies [18] or health-related quality-of-life measurements [19]. However, the differences in organ involvement in small-vessel vs. LVV is a major concern and common major manifestations of small-vessel disease, such as pulmonary, renal, or cutaneous disease are rare in TAK. Therefore, the use of BVAS may lead to unnecessary organ evaluation for LVV, whereas cardiovascular findings may be underinvestigated [12]. Furthermore, the absence of incorporation of imaging data is highly problematic. Overall, the BVAS system for disease assessment is widely considered insufficient for use in research in TAK.

The Indian Takayasu Clinical Activity Score (ITAS2010) was an attempt to develop a disease activity score for TAK [20■■]. During the development stage of ITAS2010, a disease-extent index for TAK (DEI.Tak) with 71 items was created using BVAS as the template [21]. ITAS2010 mainly evaluates the clinical features of the vascular disease (weighted more than other items) newly present in the prior 3 months as assessed by the physician (except evidence of blocked vessels documented by vascular imaging for determining pulse losses) [22]. ITAS2010 has good comprehensiveness and the interrater agreement is better than a physician’s global assessment (PGA). However, convergent validity, when assessed by comparison to PGA, is quite low at the initial evaluation. Investigators made a further attempt to incorporate APR into the score (ITAS2010-A) by adding an extra 1–3 points for an elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). However, when ‘response to change’ was assessed, patients still had high ITAS2010-A scores even when they were considered to be clinically inactive with PGA [22].

The major means in ITAS2010 for assessment of new vascular signs is physical examination. However, the limitations of physical examination were recently shown in a study [23] comparing physical examination findings with imaging data. Abnormal 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 physicians’ decision processes. Elevated APRs and especially new findings in vascular imaging studies are usually accepted to be indicative of active disease in TAK. The low correlation of ITAS2010 with PGA suggests that physicians may accept some patients as ‘active’ only with increased APR or new abnormalities on vascular imaging studies [21].

IMAGING STUDIES AS OUTCOME MEASURES IN TAKAYASU'S ARTERITIS

The ability to use radiologic imaging to examine large arteries for stenoses, occlusions, and aneurysms is critical to the assessment of TAK. The use of imaging in vasculitis is reviewed elsewhere in this issue of *Current Opinion in Rheumatology* so this section is purposefully brief. However, the potential for imaging to play an increasingly central role in disease assessment in LVV is exciting. Imaging, including conventional catheter-based dye angiography, MRI, magnetic resonance angiography (MRA), computed tomography (CT), 18-FDG-PET, and ultrasound are all imaging modalities of great interest to clinicians and investigators studying LVV [2]. These imaging techniques are able to provide good to excellent information about lumenal disease (narrowing and dilation) that is reproducible and has become a key aspect of management of LVV in those countries with ready access to these techniques [24]. However, the validity and utility of MRI or 18-FDG-PET to measure the degree of inflammation and disease activity by studying wall enhancement or other parameters remain highly controversial [25–27].

In a recent study [28■], a quantitative scoring system using color Doppler ultrasound (CDUS) was suggested for use in assessing TAK, based on the presence of stenosis and altered flow patterns in 19 sites. A high correlation was observed between angiography and Ultrasound scores, but intrathoracic vessels such as the commonly involved subclavian arteries were especially difficult to visualize and produced the lowest kappa values in this study. CDUS scores were recorded as a dichotomously value (0 and 1), thus limiting the assessment of further changes in the vessel lumen. Recently, carotid intima media thickness (CIMT), a standard surrogate marker of cardiovascular risk, was shown to be increased in patients with TAK [29]. Thoracic aorta calcifications and carotid artery plaques are also more commonly observed in TAK [30■], suggesting that atherosclerosis should be closely monitored [31].

Much ongoing research is being conducted to determine how to best use imaging in the management of TAK and for use in clinical trials. It is almost certain that imaging will be a central part of the core set of outcomes for LVV.

BIOMARKERS

Measurement of APR, such as with ESR or CRP, is frequently advocated for disease assessment in TAK despite being shown to be neither sensitive nor specific enough to monitor disease activity [2]. Serum autoantibodies such as antiendothelial cell antibodies, circulating endothelial cells, and serum biomarkers such as Vascular endothelial growth factor, interleukin-6, interleukin-8, interleukin-18, matrix metalloproteinase-9, and adipokines have each been investigated in TAK as possible surrogate markers for disease activity with inconclusive results [32–35,36■,37]. Recently, Pentraxin3 (PTX-3) levels have been reported to be associated with active disease; however, these data also require confirmatory studies [38,39]. Therefore, there are no currently available biomarkers of disease activity in TAK that are validated and proven useful for clinical care or clinical trials.

PATIENT-REPORTED OUTCOMES IN TAKAYASU'S ARTERITIS

Patients' perceptions of a vasculitis as a chronic disease interfering with general health, work status, and family and social life are often different from the physicians' approach to TAK as a vessel blockage resulting only in ischemia [40–42]. PROs are increasingly recognized as necessary outcomes in clinical trials in rheumatology. Given that patients with ANCA-associated vasculitis experience some disease-associated manifestations that are not captured by physician-based measures substantially affecting their lives and that PROs have an ability to discriminate different disease states in ANCA-associated vasculitis, the OMERACT LVV Task Force decided to plan for PROs to be in the core set of outcome measures and keep the development of PROs in TAK in the research agenda [43] (Aydin SZ, J Rheumatol, in press).

Currently, there are no disease-specific outcome tools to assess patients' perspective in LVV. General instruments such as the SF-36 have been tested in TAK and these studies [44■,45,46] found that patients with TAK have impaired health-related quality of life. In a study of a large cohort of patients with TAK in Turkey, anxiety and depression were also observed to be common. Most of the SF-36 subgroup parameters were worse in patients with active disease and patients having anxiety and depression reported worse SF-36 scores [44■]. In a further study [47], presence of fibromyalgia syndrome was more frequent in patients with active TAK and the new fibromyalgia syndrome criteria subscales (widespread pain index, symptom severity score) were significantly correlated with the SF-36 anxiety and depression scales, suggesting, again, the substantial impact of the disease on patients' well-being [47].

The OMERACT Vasculitis Working Group has conducted patient focus groups and individual patient interviews to assess the impact of TAK and treatment for the disease on the patients' quality of life (unpublished data). The preliminary results indicate that fatigue, constitutional symptoms, extremity pain/weakness, impairment of physical and social functioning, and anxiety were major issues of concern to the patients.

Given the lack of consensus on definitions to assess disease activity in LVV, the OMERACT LVV Task Force initiated an International Delphi exercise (manuscript in preparation) to ask an international, multispecialty group of experts to choose among manifestations for use in disease activity assessment tools in TAK and giant-cell arteritis (GCA). The majority of the items on the final list were considered suitable for use in clinical trials for both diseases. The group decided to start with one tool to assess disease activity for both GCA and TAK, collect data for each disease, and consider later whether two versions of an LVV instrument would be needed.

The OMERACT 2.0 Filter requires considering four areas of 'impact of health conditions' when developing outcome measures: death, life impact, resource utilization, and pathophysiological manifestations [48]. Unlike some other vasculitides, death is not a frequent outcome in LVV. The OMERACT LVV Task force is working on a research agenda that will lead to developing a core set of outcomes for LVV that will certainly include assessment of disease activity, disease-related damage, and PROs. The process will include

considering the utility of the measures outlined above, the results of the Delphi, likely drafting and testing new tools, and having investigators, clinicians, and patients working collaboratively.

DAMAGE AS AN OUTCOME TOOL

As in other inflammatory rheumatologic diseases, long-term morbidity and mortality of TAK are associated with the damage associated with disease activity, therapies or comorbidities. Damage assessment is in the core set of outcome measures for Anca-associated vasculitis, with a validated tool being the vasculitis damage index [17]. Although not published yet, a Takayasu arteritis damage score was also used in two recent clinical series [7■,49■] and other approaches to damage assessment are under consideration.

One of the major difficulties in LVV is the differentiation between activity and damage. A vascular stenosis may be due to the inflammation taking place in an acute-phase-elevated early state; however, it may also be a sign of an ongoing narrowing of the vessel wall in longstanding disease or the result of scarring. Damage is not a well studied domain in LVV and some items suggested through the Delphi exercise may not distinguish disease activity from damage. Further research will be needed to test such discrimination of outcome tools.

A time construct is also an important aspect to take into consideration when designing clinical studies. Constitutional symptoms may be quite responsive to change and therefore response can be assessed quickly, whereas imaging findings such as stenosis may have a more delayed response. Domains in a core set for use in clinical trials need to be sensitive to change and the duration of a study needs to be determined based on the main outcome of the trial.

CONCLUSION

Although outcome measures are not sufficiently validated, progress in the assessment of TAK is reflected in recent studies [49■,50] in which clinical manifestations, APR, and serial noninvasive imaging were used in combination for measuring response and to predict prognosis, especially in patients treated with biological agents (Table 1). However, recent progress in management also requires better disease assessment tools for clinical studies [11■]. Efforts of the vasculitis community in which physicians, patients, and industry representatives partner in research are expected to provide tools that will cover multiple aspects of the chronic disease process in TAK and will address the priorities of patients [40].

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KEY POINTS

- Current assessment of Takayasu's arteritis, mostly with clinical features, APR and different imaging modalities is useful for routine care, but better, validated tools are necessary for clinical trials.
- Current tools such as ITAS2010 only partially reflect physician's global assessment and management decisions and require further studies.
- Several different aspects of disease assessment such as PROs or damage should be incorporated more into clinical studies.

Table 1.

Disease assessment methods for Takayasu's arteritis

Outcome	Advantages	Disadvantages
TAK-related outcomes		
PGA	Feasible, gold standard	Not sufficiently discriminative for activity assessment, not validated
Flare	Feasible	Not sufficiently discriminative for activity assessment
Remission	Feasible	Not sufficiently discriminative for activity assessment
	Feasible	Not sufficiently discriminative for activity assessment, not validated
TAK disease activity scale (DEI.TAK/ITAS2010)	Feasible	Not in good concordance with PGA
		Not sufficiently studied
BVAS	Feasible	Missing aspects of disease
	Consistent with other vasculitides	Poorly accepted by investigators and not well validated for Takayasu's
Vascular interventions (angioplasty, stents, surgery)	Major outcome – possibly well associated with long-term prognosis	Not sufficiently sensitive for activity/damage assessment
Catheter-based angiography	Accurate assessment of vessel changes	Not feasible for routine follow-up
CT or MRA	Accurate assessment of vessel changes	Expensive
		Not validated
PET	Whole-body imaging	Expensive
	Potential for quantification of disease activity	Not validated
Damage index (VDI, TADS)	Feasible, possibly associated with prognosis	Hard to discriminate disease vs. treatment effects
Laboratory testing outcomes		
APRs (ESR, CRP), Pentraxin-3	Feasible	Not specific
		Not validated
Other outcomes		
Mortality	Feasible	Not sufficiently discriminative as a study-end point
Patient-reported assessments	Feasible	Not validated
		Disease-specific outcome not yet developed

BVAS, Birmingham Vasculitis Activity Score; CRP, C-reactive protein; CT, computed tomography; ESR, erythrocyte sedimentation rate; MRA, magnetic resonance angiography; PGA, physician's global assessment; TADS, Takayasu arteritis damage score; TAK, Takayasu's arteritis; VDI, vasculitis damage index.