Assessment of disease activity and progression in Takayasu's arteritis

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Abstract

Takayasu's arteritis (TA) is a rare, chronic panarteritis of the aorta and its major branches presenting commonly in young ages. Physical examination findings, presence of constitutional features, elevated acute-phase reactants, and new vessel involvement in imaging are major features of an active disease. However, assessment of disease activity and damage in TA is problematic given the chronic, indolent disease course and lack of specific laboratory and imaging findings. Although CT, MRI, and FDG-PET are commonly used imaging modalities, their lack of specificity to discriminate active disease from damage, limit their usefulness in routine practice. Two recently introduced multi-systemic clinical assessment tools, the DEI.Tak and the ITAS (both derived from BVAS), seem to be helpful in assessing disease activity and damage in TA. However, physician's global assessments of disease activity and decisions regarding treatments are still strongly influenced by changes in the acute-phase response and imaging. A comprehensive approach to both systemic and vascular features of TA to define a validated set of outcome measures for use in clinical trials and clinical practice is clearly needed. The OMERACT Vasculitis Working Group has taken on this task and has embarked on a research agenda to advance outcome measure development in TA.

Keywords

vasculitis; assessment; outcomes; Takayasu's arteritis

Introduction

Takayasu's arteritis (TA) is a rare, chronic panarteritis of the aorta and its major branches presenting commonly in young ages (1). Although all large arteries can be affected, the aorta, subclavian and carotid arteries are most commonly involved (60–90%) (2, 3). Arterial stenosis, occlusion, and aneurysms lead to various signs and symptoms such as extremity pain, claudication, light-headedness, bruits, absent or diminished pulses and loss of blood pressure. Although TA may present with acute events such as visual loss or stroke, it may also cause non-specific constitutional features such as fever, malaise, anorexia, and weight-loss.

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Prognosis

TA often has a protracted clinical course, and relapses are common (4, 5). The concept of remission is not clear and it is hard to define a phase when the disease is inactive (6). In one series, a significant majority of patients thought to be in clinical remission (61%) were found to have abnormalities in serial angiograms (2). Additionally, four out of nine arterial specimens obtained during arterial procedures in patients with apparent clinical remission had vasculitic features (2). Compromised daily activities are reported in 74% and loss of work in 23% of the patients with Takayasu's suggesting the high impact of the disease on daily life (2, 7). Surgical interventions and mortality figures vary according to geographical regions, possibly reflecting differences in both treatment approaches and genetics (1, 5, 8). In Japan, India, Mexico, and Turkey, the rates for surgery or percutaneous transluminal angioplasty (PTCA) (12–26%) are lower than rates in series from Italy and the USA (48–50%) (2, 3, 7, 9-12). Survival rates in more recent series were higher: 80% (1957–1975) to 96% (1976-1990) at 15 years in Japan; 94% at 7 years in Turkey, and 97% at 3–5 years in the USA (2, 3, 7, 9).

Treatment

To date no controlled clinical therapeutic trials have been performed in TA. The state of knowledge, combined with the low incidence of these disorders, and uncertainty of how to best design clinical trials and which outcome measures to use, are all important contributing factors to the lack of clinical trials in TA. Therapeutic studies in TA have been confined to small, open-label protocols or case-series, usually with a focus on the potential glucocorticoid-sparing effect of immunosuppressive agents (13-16). The paucity of treatment trials for TA is highlighted by the recently published EULAR guidelines for large vessel vasculitides (LVV), in which all treatment recommendations for TA only have an evidence level of 3 and a strength of C (17). At present, one randomised, controlled study is in progress (18) (NCT00556439).

Disease assessment in TA: current approaches

Physical examination

Physical examination for new vascular signs is a simple approach and is the first step for disease assessment in TA. However, the limitations of physical examination was recently shown in a study comparing physical signs with imaging data (19). When bruits, absent pulses, or blood pressure differences are evaluated as physical signs, the presence of any single item had a sensitivity of 52–71% and a specificity of 59–86%. Although specificity was higher if two abnormal exam findings were present (88–100%), the sensitivity of pairs of exam findings was low (6–30%). Presence of ischaemic symptoms or even signs may not always indicate active inflammation of the vessel wall (6).

Laboratory – role of acute-phase response

Acute-phase response (erythrocytesedimentation rate (ESR) and C-reactive protein) is frequently advocated for use in disease assessment in TA (20), despite being shown to be neither sensitive nor specific enough to monitor disease activity in TA (1, 21). In one study, active disease was present in the setting of normal laboratory parameters in 23% of patients with TA (7). Similarly, ESR was elevated in only 72% of patients considered to have active disease and was still high in 44% of patients considered to have inactive disease (2). Serum autoantibodies such as anti-aorta or anti-endothelial antibodies (22-24) and serum biomarkers such as IL-6, IL-8, IL-18 and BAFF (25-28) have been suggested to be related to active disease in TA; however, these data require confirmatory studies.

Imaging in TA

The use of various imaging techniques in TA has recently been extensively reviewed (1, 29-32). Any non-invasive imaging method should ideally provide accurate assessment of intra-arterial disease-related damage (occlusions, stenoses and aneurysms), measure inflammatory disease activity in the vessel wall, and distinguish inflammation from atherosclerosis. Change in imaging findings is an important aspect of demonstrating therapies. No current imaging modality has been shown to sufficiently cover all of these issues. Intra-arterial catheter-based dye angiography has long been the "gold-standard" in vascular imaging but is increasingly being replaced by magnetic resonance angiography (MRA), computerised tomography angiography (CTA), and positron emission tomography (PET) scanning.

– CTA/MRA

Contrast-enhanced MRA or CTA allow non-invasive imaging of the entire aorta and its major branches. A few studies have proposed the role of CT angiography in evaluating disease activity and monitoring disease course after immunosuppressive therapy (33-35). However, exposure to large amounts of radiation and iodinated contrast limits the usefulness of CTA in routine follow-up (32).

In addition to assessing lumen stenosis, MRA provides information about vessel wall thickness, oedema, and contrast enhancement (29). It is hoped that such data correspond to vascular inflammation, and that serial change in arterial wall parameters would correlate with disease activity and measure response to immunosuppressive therapy. Although early data indicated great promise for MRA as a disease activity marker in TA (30), further studies raised questions about both the sensitivity and specificity, discrimination between clinically active and inactive patients, and correlation between acute-phase reactants and vessel wall oedema (36-38). High-quality MRA of the arterial wall and the lumen also requires specialised equipment, and validated and standard acquisition and interpretation protocols are not yet available. Thus, while of great utility for assessment of luminal status (stenoses, aneurysms), more research is needed to define the role of CTA and MRA as disease activity measures in TA.

– FDG-PET

18F-fluordeoxyglucose-positron emission tomography (FDG-PET) scanning has become a useful non-invasive metabolic imaging modality for evaluating patients with fever of unknown origin and in staging lung cancer (39, 40). 18F-fluordeoxyglucose, accumulating in hypermetabolic cells, enables visualisation of the regional distribution in the vascular tree. As was the case with MRA, preliminary work with PET in TA suggested a high sensitivity and specificity for measuring disease activity (41, 42); however, later studies reported more disappointing results for both disease activity measurement (43, 44) and diagnosis in TA (45, 46). Studies of PET in TA have been limited by small sample sizes and there is a need to show differentiation in signal between arteritis and atherosclerosis (47). Ongoing studies of PET as a disease activity measure in TA will help define the role of this promising imaging modality.

In an attempt to overcome some of the perceived problems with FDG-PET to study large vessel vasculitis, novel ligands are under investigation. (^{11}C) PK11195 is a new ligand that binds to peripheral benzodiazepine receptors and is highly present in activated monocyte/macrophages (1). In a preliminary study, increased vascular uptake of (^{11}C) PK11195 was observed only in patients with seemingly clinically active LVV (48).

– Ultrasonography

The role of ultrasonography (US) is less established in TA compared to other modalities (4). Doppler US performs well for carotid lesions with high sensitivity (90%) and specificity (91%) (49) in detecting stenotic lesions. However, aortic and subclavian arteries are much more difficult to visualise by US with poorer detection of lesions. US may also help in determining inflammatory activity, demonstrating hypoechogenicity and mural thickening in active lesions (50). Increased arterial stiffness, an independent risk factor and predictor of cardiovascular mortality in various diseases, atherosclerotic plaques, and intima-media thickness have been observed with US in several studies in TA (51-53). However, no association with disease activity or acute-phase reactants was demonstrated. The possible role of US for disease assessment and cardiovascular morbidity in TA requires further study.

Current status of outcome measures for use in TA

Disease assessment in TA requires the evaluation of both vascular and constitutional features. Research directly focused on outcome measures in TA has been limited. Despite the many cohort studies published, there are no fully-validated outcome measures for use in clinical trials in TA. Few studies have focused on applying tools already in use in other diseases to TA and none of these projects have resulted in tools validated for TA. However, some useful information and insight into outcome measures can be obtained by reviewing the methods used for disease assessment in published clinical trials and cohort studies.

There have been many different outcomes used to study TA. The simple definition of "active disease" that was included in a study from the National Institute of Health (NIH): presence of constitutional symptoms, new-bruits, acute-phase response or new angiographic features is commonly applied (2). A comprehensive review of the medical literature of TA using the keywords "outcome, activity, relapse, remission and assessment" resulted in 73 clinical research articles; a summary of the frequency of use of different outcome measures in these studies is shown Table I (54). The four items in the NIH series were used by most studies to define "active" disease. Activity defined by imaging only (MRI, PET or CT) was primarily used in imaging studies. Remission (19%) or relapse (6%) were also defined in a limited subset of studies.

Measures of disease activity in TA

The Birmingham Vasculitis Activity Score (BVAS) documents evidence of active vasculitis on a one-page form (55). Although designed to apply to all vasculitides, BVAS is mostly used in therapeutic trials of ANCA-associated vasculitis and is validated for use in small and medium-vessel vasculitis. However, most of the 11 organ systems in BVAS are not involved in TA (56). Only two studies in TA have used BVAS (57, 58).

The "disease extent index for Takayasu's arteritis (DEI.Tak)" is a recently-developed assessment tool in which items corresponding to large arterial disease carry greater weights than general items of the disease, and changes in the prior 3 months in the physical examination are the basis of evaluation (59). In a study from Turkey of patients with TA, most patients with slow progression of disease demonstrated no change in the DEI.Tak score (56). Because the DEI.Tak was substantially derived from the BVAS, most items are related to small-vessel vasculitis and these items were not involved or did not change in the patients with TA. Furthermore, discriminant ability of the instrument was not high; among the DEI.Tak (-) group, 31% were felt to have "active/persistent" disease according to the physician's global assessment (PGA) while 18% of patients with a DEI.Tak score 1 were considered inactive by PGA. Although patients with active or persistent disease had higher DEI.Tak compared to patients with inactive disease, PGA and DEI.Tak had only modest agreement (68%). Another cohort study of a DEI.Tak found similar results (60). These

studies raise concerns about the sensitivity to change of DEI.Tak. Another issue is whether DEI.Tak discriminates sufficiently between disease activity and disease-related damage.

Recently, a new version of DEI.Tak, the Indian Takayasu's Arteritis Score (ITAS) was introduced (61). ITAS has only 6 systems and scoring is weighted for vascular items (0-2). DEI.Tak and ITAS seem to have a good correlation; however, the correlation between the PGA and ITAS is poor *(Yılmaz et al., personal communication)*. The ITAS has been used in a clinical trial of TA (16). Thus, while there is a strong need for disease activity measures in TA, there are no validated instruments to measure this domain of illness in TA. Future work will focus on development of validated, disease-specific measures in TA (54).

Measures of disease-related damage and mortality in TA

Treatment for TA is focused on the prevention of disease-related damage (62, 63) and the effects of arterial disease and treatment toxicities are the major cause of morbidity for patients with TA. Large arterial disease in TA often leads to irreversible vascular occlusion, and some cases require surgical intervention. It is critical to differentiate irreversible damage from disease activity and thus avoid potential over-treatment with toxic agents. Furthermore, treatment decisions in the care of patients with TA depend heavily on damage assessment. Physicians are often prompted to escalate and/or change therapies by a change in "damage" (*i.e.* new stenosis) rather than the measurement of disease activity.

Although the Vasculitis Damage Index (VDI) has been the standard tool for assessing damage in small vessel vasculitis, data supporting its use in TA is not present (64). There is considerable uncertainly about the utility of the VDI in TA, as for example, physician decisions with the VDI rely upon physician global assessment which is strongly influenced by imaging data and acute-phase reactant levels.

The data on mortality in TA is limited but the mortality appears to be increased (65). The current TA mortality rates (3–15%) reflect series with different treatment approaches and follow-up periods (2, 3, 7, 9-11, 13, 66). Mortality is unlikely to be the major outcome measure for clinical trials in TA.

Measuring health-related quality of life in TA

Disease-related damage and treatment toxicity in TA can severely impact patients' quality of life and functional status. Thus, it is important to measure the health-related quality of life (HRQOL) in patients with TA and determine the effect of treatments on this domain of illness. It has been shown that patients with vasculitis judge the importance of various disease manifestations differently from how physicians rate the same problems (62, 63). Two studies have used the Short-Form 36 (SF-36) to measure HRQOL in TA (67, 68) finding that patients with TA had reduced SF-36 scores (implying reduced quality of life). The utility of measurements of HRQOL in clinical research in TA requires additional study, but it is likely that such outcomes will complement physician-based measures.

Differentiating TA from atherosclerosis

Although, differentiation of TA lesions from atherosclerotic plaques is of less concern in a typical, young female patient, given the highly indolent clinical course, the diagnosis in older ages, and the better long-term outcomes, it is crucial to distinguish between vasculitis and atherosclerosis (32). Features such as vessel distribution (*e.g.* subclavian involvement mainly in TA and lower abdominal aorta in atherosclerosis), luminal and lesional appearance (*e.g.* smooth *vs.* irregular thickening), and imaging characteristics are helpful. However, issues such as increased vascular uptake on PET in the elderly (47), possible

"accelerated" atherosclerosis in TA, especially in cranial vessels (53), and microemboli in middle cerebral arteries (69) complicate the interpretation of imaging data. Whether new imaging modalities will help in individual patients needs to be studied.

Conclusions

Disease assessment in TA is quite difficult, and the disease is among the least studied vasculitides. General activity is defined broadly with the presence of categorical definitions: constitutional symptoms, new-bruits, acute-phase response, or new angiographic features. However, no highly reliable associations are present among the physical examination findings, laboratory or imaging outcomes, and physician-defined "disease activity" measures. There is a clear need for developing a validated set of outcome measures for TA for use in clinical trials and clinical practice. The OMERACT Vasculitis Working Group has taken on this task and drafted a research agenda (54).

Acknowledgments

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Table I

Summary of outcome measures used in trials of Takayasu's arteritis by study type.

Outcome	Treatment and outcome series (n=34) (%)	Imaging[*] (n=15)(%)	Biomarker studies (n=24)(%)	Overall (n=73)(%)
Takayasu's arteritis-related outcomes				
Remission	7 (21%)	0 (0%)	7 (29%)	14(19%)
Relapse	3 (9%)	0 (0%)	1 (4%)	4 (6%)
Stable	4 (12%)	0 (0%)	1 (4%)	5 (7%)
Activity according to the definition by Kerr *et al.*	14 (41%)	8 (53%)	11 (46%)	36 (49%)
TAK disease activity scale (DEI.TAK/ ITAS)	2 (6%)	0 (0%)	0 (0%)	2 (3%)
Interventions (PTCA+surgery)	23 (68%)	1 (7%)	1 (4%)	25 (34%)
Laboratory testing outcomes				
ESR, CRP or CBC	23 (68%)	12 (80%)	21 (88%)	56 (77%)
Glucocorticoid-related outcomes				
Dose or duration	25 (96%)	7 (54)	17 (74%)	49 (79%)
Other outcomes				
Mortality	13 (46%)	0 (0%)	0 (0%)	13 (20%)
Patient-reported assessments	3 (11%)	0 (0%)	0 (0%)	3 (5%)
Angiography	21 (62%)	8 (53%)	11 (46%)	40 (55%)

n = the number of studies reporting the listed outcome parameter.

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[*] studies on imaging modalities other than conventional angiography.