Clinical assessment in Takayasu’s arteritis: major challenges and controversies

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Received on March 2, 2017; accepted on March 8, 2017.


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Key words: Takayasu’s arteritis, clinical assessment, outcome

ABSTRACT

Takayasu’s arteritis (TAK) is a rare, chronic, large-vessel vasculitis (LVV) that predominantly affects aorta, its major branches and the pulmonary arteries. Recent controversial issues in the diagnosis, disease assessment and prognosis in TAK are discussed in this review. In recent years, conventional angiography, the standard method for the initial diagnosis, seems to have been replaced by the new imaging modalities, such as MRI and 18F-FDG-PET. Less invasive techniques (CT/MRI) are now suggested first, compared to conventional angiography, and MRI is preferable to CT with less contrast load/radiation. Ultrasound is useful for carotid assessment, but being a user-dependent technique, imaging of deeper vessels (subclavian and aorta) are not reliable. 18F-FDG-PET is useful especially in patients with no vascular symptoms/signs, fever of unknown origin or unexplained acute-phase response. MRI and 18F-FDG-PET are also promising for the assessment of disease activity. New tools for disease assessment such as Indian Takayasu Arteritis Score (ITAS2010) aim to better characterise and quantify disease activity. Prognosis is recently possibly getting better with lower mortality, but a substantial damage is present even in early cases. There is a clear need to develop a validated set of outcome measures to be used in clinical trials of TAK. The OMERACT Vasculitis Working Group has taken on this task, finished a Delphi exercise with experts and aims to develop a core set of outcomes for LVV.

Introduction

Takayasu’s arteritis (TAK) is a rare, chronic, large-vessel vasculitis (LVV) that predominantly affects aorta, its major branches and the pulmonary arteries (1). Segmental stenosis, occlusion, dilatation or aneurysm formation may occur in the vessel wall during the course of the disease. All large arteries can be affected, but most frequently involved are ascending/descending aorta, subclavian and extra-cranial arteries such as carotids (60-90%) (2-4). Small- or medium-sized vessels are rarely involved. Onset is usually below 50 years of age with an overwhelming female dominance. The disease generally has a prolonged, indolent course and acute events such as visual loss or stroke are rare in TAK. In this review, recent advances and controversial issues in the clinical assessment of TAK will be discussed.

Diagnosis and classification issues

Lack of a tissue biopsy or a specific autoantibody, along with the non-specific nature of imaging studies or acute-phase reactants (APR), make the diagnosis of Takayasu’s arteritis a challenging clinical issue. Classification criteria for TAK were established by the American College of Rheumatology in 1990 (5). Although these criteria have not been criticised much as other ACR criteria sets (such as polyarteritis nodosa) with over 90% sensitivity and 97% specificity in the original cohort, the control group formed by mainly small-vessel vasculitides (used for similar ACR 1990 classification criteria sets) which have limited common clinical features with TAK. The usefulness of these criteria is therefore limited in real-life setting, in differentiation from atherosclerotic or congenital aortic vessel disease, especially in the middle-aged population. Subclavian stenosis (seen in up to 80% cases with TAK), associated with atherosclerotic disease, is present in up to 5.1% of females when investigated in the general population without symptoms (6). Although the differences in vascular pattern of involvement is usually prominent (7, 8), some series suggest
an overlap between giant cell arteritis (GCA) and TAK (9) and new entities such as IgG4-related diseases involving aorta make the discrimination among LVV subsets even more difficult. In a recent series from Mayo Clinics, each item in the 1990 classification criteria (except imaging) was present in only 52–75% of the cases and a high sensitivity is only achieved when an age cut-off of 50 years and the exclusion of GCA is used (10). In the recently completed first controlled therapeutic trial of a biologic agent in TAK, an angiographic abnormality compatible with TAK and shown by an angiographic method is required for inclusion (11). To overcome these problems, a global Project, Diagnostic and Classification in Vasculitis Study (DCVAS) is underway to form new classification criteria for all vasculitides (12). For DCVAS, a large control group including vasculitis-mimics will also be evaluated.

**Disease assessment: major challenges**

Assessment of the pattern and extent of arterial involvement and measurement of current inflammatory status are essential for the optimal medical and interventional management of TAK (13). However, the lack of a “gold standard” for disease activity in TAK presents a major challenge in creating useful and valid outcome tools for the assessment of disease course. One of the major difficulties is the differentiation between activity versus damage in LVV. A vascular stenosis may be due to the inflammation if is taking place in an acute phase-elevated early state, however may also be a sign of an ongoing atherosclerotic/inflammatory narrowing of the vessel wall in longstanding disease or the result of scarring. Multiple empiric definitions of “remission/relapse” or ‘activity’ defined by clinical features, based on biomarkers (acute-phase response) or vascular imaging have been proposed and seem sufficient for drug trials as the “primary outcome” (11, 13). However various other aspects of disease course such as damage or patient-derived outcomes are insufficiently explored until now (14).

The most commonly adopted approach for ‘disease activity’ is the simple definition originally used in a study from US National Institute of Health (NIH) with the presence of any two of: constitutional symptoms, new-bruits, elevated acute-phase reactants or new angiographic features (2). A literature search performed for TAK have shown that items in this NIH series were preferred by almost half of the studies to define active disease (15).

**Imaging in TAK**

Conventional digital subtraction angiography (DSA) is the “gold standard” for detecting stenosis, occlusions and aneurysms that characterise the late stages of TAK and is the most reliable method for lumen assessment (1). It also allows aortic pressure measurement and imaging of coronary arteries suitable for radiological intervention. The typical angiographic finding is the presence of “skip lesions”. Lesions are usually observed close to the origin of the primary branches of the aorta and earliest lesions are localised narrowing or irregularities of the arterial lumen which may progress to stenosis, occlusion or aneurysm formation. However, DSA is invasive, difficult to repeat and have a high contrast load. It may be normal in early disease, as it is the least sensitive method for visualising wall thickness (16).

**CT/MRI**

Contrast-enhanced MR-imaging/angiography (MRT/MRA) or CT angiography (CTA) allow non-invasive imaging of the aorta and its major branches. CTA has a high resolution with a short scanning time. It also demonstrates calcifications which are observed more frequently in atherosclerotic lesions. It is minimally invasive, repeatable and inexpensive. However, high radiation load limits its use in the long-term (17).

Recently, MRA has become popular for the diagnosis of TAK. Compared to invasive angiography, three-dimensional MRA can effectively show vessel wall thickening (16, 17). Contrast-enhanced MRA allows better soft-tissue differentiation and can also depict other signs of inflammation, including mural oedema and increased mural vascularity. Another advantage of MRA is the lack of iodinated contrast material. MRA is extensively investigated in the current literature for evaluating vascular inflammation and increasingly replaced invasive angiography. Although MRA appears to be both highly accurate, sensitive and safer compared to invasive angiography in the diagnosis of TAK, approximately 2% of stenotic arteries were wrongly portrayed as occluded. Some recent studies have suggested that MRA technology has also the potential to assess the disease activity and response to treatment. Contrast-enhanced MRI detects oedema and enhancement of vascular wall, as well as a reduction of the mural diameter on MR images, associated with disease activity (18, 19). Furthermore, these studies suggest that there is a close correlation between wall thickness and/or oedema of the vessel, enhancement of wall detected by MR imaging and acute-phase response. However, some other studies showed no major MRA differences between active and inactive disease (20, 21).

**18F-FDG PET**

Positron emission tomography (PET), a modality based on the regional distribution of the glucose analogue 18F-fluorodeoxyglucose (FDG), is an operator independent, non-invasive metabolic imaging method. Immune cells (macrophages etc) uptake 18F-FDG, especially when activated and 18F-FDG is trapped inside the cells (16,17). Assessment is done after 6 hours of fasting and the blood glucose <160 mg/dl. 18F-FDG PET is a sensitive and specific imaging tool for large-vessel vasculitis. There are three main methods of assessment with 18F-FDG uptake. Qualitative visual method is an expert opinion based, non-quantitative visual assessment. In visual scoring, a semi-quantitative analysis is applied, comparing the 18F-FDG uptake of a vascular region of interest (ROI) with that of the liver with a 0–3 grading (0 = no uptake present - III = high-grade uptake (uptake higher than liver uptake). In semi-quantitative method direct aorta standart uptake (SUV) or aorta/liver/ sup-inferior vena cava or pulmonary
artery ratios are calculated. In a meta-analysis of the literature using seven studies, the pooled sensitivity and specificity of 18-FDG-PET is observed to be 87% and 73% for the assessment of disease activity in TAK (22). However, there are important methodological problems that need to be standardised before 18-FDG-PET studies can be comparable. Liver SUVs are quite variable (SUVs 2–4) according to the presence of hepatosteatosis, corticosteroid use and the severity of inflammation. In visual assessment, it is not clear whether the cut-off should be equal to or higher than liver SUVs. In a study of GCA with LVV, it was shown that when SUV values equal or higher is used, sensitivity is excellent (100%), however specificity drops to 67%, whereas with only values higher than liver as the cut-off, sensitivity versus specificity is more acceptable (83% and 91%, respectively) (23). There is a significant uptake also in atherosclerotic plaques and corticosteroid use may cause false negative results.

Recently, we have compared whether an aorta/liver SUV maximum or mean ratios give a better area under the curve (AUC) values in TAK (24). Use of liver maximum provided 72% specificity and sensitivity with AUC: 0.728, whereas use of liver mean values had a 71% sensitivity and 79% specificity, with an AUC of 0.695. In this study, 18-FDG-PET was not sufficiently discriminative between low-level disease activity (increased APR or limited clinical activity) and remission, suggesting that clear definitions of active/inactive disease should first be defined. Both multi-centre clinical studies and expert review is necessary and a EULAR task continues. Acute-phase response (erythrocyte sedimentation rate (ESR) and C-reactive protein) is frequently advocated for disease assessment in TAK, despite being shown to be neither sensitive nor specific enough to monitor disease activity. Serum biomarkers such as IL-6, IL-8, IL-18, matrix metalloproteinase-9, VEGF and circulating endothelial progenitor cells are previously suggested to be as candidate biomarkers (4, 27, 28). Recently Pentraxin-3 (PTX3) which is produced by immune and vascular cells in response to proinflammatory signals, is suggested as a biomarker for disease activity in patients with TAK. In a single centre study from Italy, levels of PTX3 were higher in patients with active TAK (median, >2.14 ng/mL) than in inactives (0.63 ng/mL), patients with infections (0.26 ng/mL) and healthy controls (0.11 ng/mL) (29). In another study from Japan, Among the 28 patients with active TAK, 71% was positive for hsCRP and 82% for PTX3 (30). However, we could not demonstrate a discriminative value of PTX-3 levels in our Turkish cohort (31), and in another Italian study, PTX-3 levels were similar between active versus inactive patients and only CRP was higher in active disease (32). As a new observation, this study found significantly higher PTX-3 levels in a subset of patients showing detectable signs of vascular inflammation by vascular imaging, suggesting that PTX-3 may reflect different aspects of inflammation than CRP and might represent a biomarker of actual arteritis in TAK.

**Composite outcome measure in TAK**

The Birmingham Vasculitis Activity Score (BVAS) is a practical, one-page score to document the clinical activity of vasculitis. Although designed for all vasculitides, BVAS is mostly used in therapeutic trials of ANCA-associated vasculitis. It is not popular with TAK studies, as most of the 11 organ systems in BVAS are not involved in TAK. Recently, a version of BVAS, the Indian Takayasu’s Arteritis Score (ITAS2010) was introduced (33). ITAS2010 has only 6 systems and scoring is weighted for vascular items (0–2). ITAS2010 seems to have a good comprehensiveness and the inter-rater agreement is better than physician’s global assessment (PGA) (0.97 vs. 0.82). However, convergent validity, when assessed by comparison to PGA, is quite low at the initial evaluation but improved at subsequent study visits (r=0.51, 0.64, and 0.72). Although CRP and ESR had weak correlations with ITAS2010, the authors also incorporated APR to...
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, and a cut-off of 4 points is suggested for a definition of active disease.

In a study of Turkish patients during routine follow-up, ITAS2010 was significantly higher in patients with active disease (34). However, total agreement between ITAS2010 and PGA was again moderate (66.4%), but was better between ITAS2010 and NIH score (82.8%). During follow-up, 14 of 15 patients showing vascular progression with imaging were categorised as having inactive disease according to ITAS2010. The low correlation of ITAS2010 with PGA suggests that physicians seem to accept some patients only with increased APR or new abnormalities on vascular imaging studies (such as new vessel wall enhancement or thickening seen by MRI or PET) as ‘active’, which were below the cut-off values of ITAS2010 for active disease.

**Outcome and prognosis**

Although prognosis in a recent Japanese series is reported to be improving, there is still a significant delay in the diagnosis of TAK and both morbidity and mortality is increased with a high rate of new, severe manifestations after diagnosis (10, 35). Secondary hypertension, congestive heart failure and longer disease duration were risk factors for mortality in a series of Chinese patients (36).

A significant subset of TAK patients (44%) developed new severe manifestations during follow-up in the VCR cohort from USA (37). In a recent series of Korean patients in remission, 22% had a relapse during a follow-up of 37 months, which is mainly associated with Type V disease, suggesting that low-level inflammation is associated with the extent of the disease (38). Interestingly, disease starting > 40 years is observed to have fewer relapses with lower initial doses of corticosteroids for remission induction in Japan (39).

As in other inflammatory disorders, accelerated atherosclerosis is a possible risk factor for increased morbidity and mortality in TAK. Atherosclerotic plaques (especially thoracic aortic calcifications) are more frequent and carotid intima-media thickness is increased in TAK (40-42). Recently, in a comparative study of patients from USA and Turkey, 10-year coronary heart disease risk score and the incidence of CVE was observed to be higher in TAK patients compared to ethnically matched controls (Alibaz-Oner et al., manuscript in preparation).

Assessment of ‘damage’ due to disease or treatments such as corticosteroids are becoming the cornerstone of long-term follow-up of vasculitis patients and part of the core set of outcome measures for AAV, with a validated tool, vasculitis damage index (VDI). In a recent series from Turkey, VDI was assessed in 165 TAK patients with a mean follow-up of 60 months (43). VDI scores in TAK were moderately high (mean: 4 (1-12)) and were mainly due to the disease itself with major vessel occlusion. Only 39% had treatment-related damage and osteoporosis/vertebral fractures were the main cause. Age, resistant disease course, disease duration and cumulative corticosteroid doses were independently associated with damage, suggesting that, even in experienced centres, accumulation of damage is a major challenge in the management of TAK patients. Although not published yet, a more-specific Takayasu arteritis damage score (TADS) from India, and a large-vessel vasculitis index of damage (LVVID) score by VCR are in the development phases.

**Conclusions**

Current classification criteria for TAK requires a better set of items to discriminate among LVV and mimics. Conventional angiography, the gold standard method for the diagnosis of TAK, seems to be replaced with the new imaging modalities such as MRI and 18F-FDG-PET in recent years. However, the optimal imaging method for follow-up and disease assessment is still controversial. Pentraxin-3 is a possible biomarker, and new quantitative tools for disease assessment such as Indian Takayasu Arteritis Score (ITAS2010) and colour Doppler ultrasonography score (CDUS) aim to better characterise and quantify disease activity.

There is a clear need to develop a validated set of outcome measures for use in clinical trials of TAK. The OMERACT Vasculitis Working Group advanced a research agenda and a Delphi exercise is completed to determine (1) experts’ consensus opinions on the disease domains and subdomains of importance to study in LVV; and (2) a preliminary set of outcomes and outcome instruments to capture data on the domains (Aydin SZ, manuscript in preparation). Further studies will explore the definitions for flare, remission and response and aim to improve disease assessment tools with expert opinion and patient data.

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