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UPDATE IN TAKAYASU'S ARTERITIS

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Abstract

Takayasu arteritis (TAK) is a rare, chronic granulomatous large-vessel arteritis affecting mainly the aorta and its major branches. Inflammation of the vessel wall causes segmental stenosis, occlusion, dilatation, and/or aneurysm formation. Although all large arteries can be affected, the aorta, subclavian, and carotid arteries are the most commonly involved TAK is mainly observed in young females. Recent advances in the diagnosis, clinical course, disease assessment, and treatment of TAK are discussed in this review. In the presence of typical symptoms and physical findings such as loss of pulses and/or decreased arterial blood pressure and elevated acute phase responses, the diagnosis should be confirmed easily by angiographic imaging modalities. Magnetic resonance angiography is the gold standard modality for both diagnosis and longitudinal follow-up of patients with TAK. In recent years, positron emission tomography (PET) has become a widely used imaging method for the diagnosis of TAK with high sensitivity. The place of PET during follow-up in TAK is still controversial and requires further studies. Prognosis is recently possibly getting better with lower mortality, but a substantial damage is present even in early cases. It is critical to differentiate irreversible damage from disease activity and thus avoid potential over treatment with toxic agents such as corticosteroids in TAK. There is a clear need to develop a validated set of outcome measures for use in clinical trials of TAK. In daily practice, routine imaging follow-up is not recommended in clinically and laboratory silent TAK patients assessed as inactive by the physician. The level of evidence for TAK management is low, and expert opinion is still the main determinant when managing patients with TAK during daily practice. Glucorticoids are the mainstay of TAK treatment. While tapering glucocoticoids, non-biologic immunosuppressive agents should be added to the treatment. Leflunomide, methotrexate, azathiopurine, or mycophenolate mofetil could be chosen as the first-line immunosuppressive agent. If there is a treatment failure with first-line agents, switching to tumor necrosis factor inhibitors or tocilizumab should be considered.

Keywords: Takayasu's arteritis, diagnosis, disease assessment, treatment

INTRODUCTION

Takayasu arteritis (TAK) is a rare, chronic granulomatous large-vessel arteritis affecting mainly the aorta and its major branches. Inflammation in the vesssel wall causes segmental stenosis, occlusion, dilatation and/or aneurysm formation. Although all large arteries can be affected, aorta, subclavian and carotid arteries are the most commonly involved arteries (60-90%) (1,2). TAK is observed worldwide. However, it is more frequently reported in East Asian countries including Japan, India, and Korea and also recently from the Middle East, especially Turkey (3). Prevelance was found 40/million in Japan and 0.9/million in the USA. Prevelance was reported as 15-33/million in Turkey (4,5). TAK is seen more 1.6-12 times more frequently in women than men (6-8). Disease onset age had a peak around 20-130 years old (8).

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Clinical Manifestations

Arterial stenosis, occlusion, and aneurysms lead to various signs and symptoms such as extremity pain, claudication, light-headedness, constitutional features (such as fever, malaise, anorexia, andloss), bruits, absent or diminished pulses, and loss of blood pressure. TAK generally follows an insidious course at onset. However, atypical and/or catastrophic disease, such as acute visual loss or stroke, may also occur. The clinical course of TAK generally has three phases. The first phase is characterized by non-specific constitutional inflammatory symptoms such as fever, weight loss, and fatigue. In the second phase, inflammation of arterial walls is prominent, causing carotidynia, neck pain, and sometimes back pain in the thoracic and dorsal areas. The third phase, thought to be the late phase of the disease, is characterized by bruits, decreased or absence of pulses, and blood pressure difference between arms and extremity claudication. During the diagnostic phase, 10-20% of patients with TAK are asymptomatic (3). Carotidynia occurs in 2-32% of patients. Stenosis or aneurysm formation in the involved arteries causes the decreased circulation. This manifests as typical intermittent claudication in the extremities. Vertebral and carotid involvement may be asymptomatic or present with transient ischemic attacks, stroke, dizziness, syncope, headache, or visual changes. Mesenteric involvement is common, but gastrointestinal symptoms such as nausea, diarrhea, vomiting, and ischemic abdominal pain are not frequently observed. Hypertension may be seen due to atypical coarctation of the aorta, aortic valve regurgitation related to aortitis, or renal artery stenosis (9,10). Cardiac involvement, mainly as aortic regurgitation, is present in approximately one-third of patients. Takayasu retinopathy and scleritis are uncommon manifestations of the disease (1-3). Cutaneous manifestations range between 3-28% of patients, and the most common manifestation is erythema nodosum (11). Joint involvement may present as arthritis and arthralgia in almost half of the patients, but it does not have a destructive pattern (12,13).

There are an increasing number of studies reporting inflammatory bowel disease and other spondyloarthropathy features in TAK (14,15). Further investigations are needed to focus on possible shared immunopathogenic or genetic processes.

Differential Diagnosis

1990 American College of Rheumatology (ACR) criteria, which are the most widely used in clinical studies, require the presence of three of six criteria to differentiate TAK from other systemic vasculitis (Table 1) (16). However, this criteria set mainly covers the late stage of disease and includes conventional angiography as the only imaging modality. In a young patient with unexplained systemic inflammation, nine red flags should remind TAK to the clinician (Table 2) (12). Involvement of subclavian arteries, especially the left side, and common/internal carotid arteries are typical for TAK. TAK lesions mostly develop in a symmetric manner in paired vascular territories, and disease extension is contiguous in the aorta (17).

One of the most important diseases in the differential diagnosis of TAK as large-vessel vasculitis is giant-cell arteritis (GCA). Disease onset in young age (<40), striking female predominence and ethnic discrimination are important differeneces of TAK. It is not always possible, especially in elderly patients with risk factors for atherosclerotic vascular disease. While the vasculitic involvement is generally located in the proximal part of vessels, atherosclerotic lesions are generally located in bifurcation sites and ostia of the vessels. In the vessel wall, vasculitic involvement leads to diffuse and homogeneous thickening, whereas atherosclerosis leads more localized, irregular and hon-homogeneous thickening. Punctat, linear calsification and patchy involvement also suggest atherosclerosis, in contrast to mural and circumferential calcification suggesting diffuse involvement in vasculitis. In the differential diagnosis of TAK,

Table 1. 1990 criteria for the classification of Takayasu arteritis

Age of 40 years or younger at disease onset
Claudication of the extremities
Decreased pulsation of one or both brachial arteries
Difference of at least 10 mmHg in systolic blood pressure between arms
Bruit over one or both subclavian arteries or the abdominal aorta
Arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the upper or lower extremities that is not due to arteriosclerosis, fibromuscular dysplasia, or other causes
At least 3 of 6 criteria are necessary for classification

Table 2. Red flags for investigating Takayasu arteritis

Carotidynia
Hypertension
Angina pectoris
Vertigo and syncope
Extremity claudication
Absent/weak peripheral pulses
Discrepant blood pressure in the upper limbs (>10 mmHg)

many rare entities leading to infectious or non-infectious aortitis should also be considered (18).

Disease Activity Assessment

Physical Examination in Clinical Activity Assessment

Physical examination for new or worsened vascular signs, such as bruits, pulse, or blood pressure difference between extremities, is the first step in TAK disease assessment. Although abnormal findings on vascular physical examination are highly associated with the presence of arterial lesions in imaging, at least 30% of arteriographic lesions can be missed with only physical examination (19).

Laboratory in Disease Activity Assessment

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels are frequently advocated for disease assessment of TAK. In one study, active disease was present in the setting of normal laboratory parameters in 23% of the patients (20). Similarly, ESR was elevated in only 72% of patients considered to have active disease and was still high in 44% of patients considered to be in remission (21). Serum autoantibodies such as anti-aorta or anti-endothelial antibodies and serum biomarkers such as of tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, IL-8, IL-18, interferon gamma, matrix metalloproteinase (MMP)-2, MMP-9, YKL-40, A proliferation-inducing ligand and B cell survival factors activation factor are shown to be elevated in TAK, but are not disease-specific. The pentraxin (PTX) superfamily is a group of proteins that recognize various exogenous pathogens and behave as acute-phase response mediators. Despite the contoversial results, PTX-3 was suggested to be a discriminative marker for active disease in TAK (22).

Outcome Measures in Disease Activity Assessment

The simple definition of "active disease" that was used in a study from the National Institute of Health (NIH): 'Presence of constitutional symptoms, new-bruits, acute phase reactants (APR) or new angiographic features' is commonly applied in clinical studies (23). Birmingham Vasculitis Activity Score (24), and the "disease extent index for Takayasu's arteritis (DEI.TAK)" were not widely accepted and used in TAK (25). In 2010, the Indian Takayasu's Arteritis Score (ITAS) was introduced. ITAS-2010 has only 6 systems and scoring is weighted for vascular items (0-2). ITAS-2010 seems to have a sufficient comprehensiveness and the inter-rater agreement is better than (Physician's Global Assessment) (0.97 vs 0.82). The authors also incorporated acute phase response to the score (ITAS-2010-A) by adding an extra 1-3 points for elevated ESR or CRP (26). ITAS-2010 became more widely used assessment tool compared to previously mentioned tools (27-29). The Outcome Measures in Rheumatology (OMERACT) Vasculitis Working Group completed a Delphi exercise to determine a consensus for candidate outcomes for disease activity assessment in large vessel vasculitis (LVV) in clinical trials, and a set of important items to measure were identified. OMERACT has been working on it (30). European League Against Rheumatism (EULAR) suggested new definitions for active disease, relapse, and remission. However, these new definitions are consensus-based and do not derive from a systematic literature review. EULAR suggests using the term 'relapse' and avoiding the term 'flare'. These definitions seem acceptable, but they need to be tested in prospective studies (31).

Prognosis and Disease Course

TAK generally has a relapsing-remitting course. There can be prolonged periods of seemingly clinically "inactive" disease during which arterial damage can still progress. Due to the lack of standardized assessment tools, physicians generally manage cases with TAK according to physician global assessment as the 'gold standart' in daily practice, combining clinical symptoms, APR, and imaging (13). Despite immunosuppressive treatments, relapses were observed in approximately one-third of TAK patients during follow-up (2,32). Accelerated atherosclerosis is an important risk factor for increased morbidity and mortality in TAK. In a comparative study of patients from USA and Turkey, cardiovascular (CV) risk factors were more common in patients with TAK, particularly hypertension (33). According to 2018 update of the EULAR recommendations for the management of LVV, aspirin should not be routinely used for treatment of LVV unless it is indicated for other reasons (31). Overall, current data suggest that patients with TAK should undergo careful assessment of CV risk factors, and an aggressive risk modification approach is warranted.

Damage Assessment in the TAK

It is critical to differentiate irreversible damage from disease activity and thus avoid potential over-treatment with toxic agents such as corticosteroids in TAK. Angiographic findings may not demonstrate whether changes in the vessel wall are associated with active vascular inflammation or irreversible damage (34). The Vasculitis Damage Index (VDI) is the standard tool for assessing damage in small vessel vasculitis (35). In a large series from Turkey, VDI scores in TAK were moderately high [mean: 4 (1-12)] and were mainly due to the disease itself with major vessel occlusion (36). Another damage score, TAK Damage Score (TADS), derived from DEI.TAK, consists of 7 categories, which are mainly focused on the CV system (37).

In a recent study comparing VDI and TADS, the median number of disease-related items was higher in TADS scoring (8 items vs 4 items) at the end of the follow-up (app. 77 months). At least 1 new corticosteroid-related damage item occurred in 35 patients (31%). The results confirmed that damage assessment with VDI seems to be predominantly evaluating treatment-related damage, whereas TADS provides more detailed information on disease-related damage in TAK (38). The large-vessel vasculitis index of damage score is used in GCA but is still in the revision process by Vasculitis Clinical Research Consortium (39).

Mortality

Although recent data is showing better prognosis in TAK, there is still a significant delay in the diagnosis of TAK. Both morbidity and mortality rates are still high because of new and severe manifestations after diagnosis (40). Overall survival was much better compared to earlier series (97% at 10 and 86% at 15 years), but mortality was still increased compared to the general population (41). In recent French series assessing 318 patients, mortality was 5% in a median follow-up of 6.1 years (42). Differences of mortality rates reported in different series may be explained by differences in disease phenotypes, medical therapy, and access to endovascular or surgical therapy.

Imaging

Angiographic imaging of vessels is necessary for both diagnosis and follow-up of TAK. Optimal imaging of vessels should visualize both the arterial lumen and the arterial wall in TAK (43). The earliest detectable sign in the vessel wall is usually thickening caused by inflammation. Wall thickness can be shown by ultrasonography, computarized tomography (CT) angiography (CTA) and magnetic resonance angiography (MRA). Conventional digital subtraction angiography (DSA) can detect stenosis, occlusions, and aneurysms, which are mostly late-stage findings of TAK. DSA has a very limited ability to detect wall thickness in TAK (1), and is not routinely recommended in recent EULAR guidelines for imaging in LVV (44).

CTA

CTA has become a widely accessible imaging tool for TAK. It is valuable for especially differentiating TAK from atherosclerosis. Circumferential aortic calcification is observed only in TAK, and this difference is quite helpful in differentiating vasculitis from atherosclerosis (45). CTA has a sensitivity higher than 90% for the diagnosis of TAK. Shorter acquisition time for CTA is an important advantage during daily practice compared with MRA. On the other hand, usage of iodinated contrast and exposure to radiation limits the usageof CTA in routine follow-up of TAK patients (46).

MRA

MRA has become the standard angiographic method for the diagnosis of TAK and is suggested as the first-choice imaging tool according to the EULAR guidelines (44). Lack of radiation exposure makes possible longitudinal imaging follow-up evaluations in patients with TAK. Thickening and enhancement in the vessel wall were suggested as the sign of active disease, and aslo reported a close correlation between wall thickness and/or edema of the vessel and APR (47,48) However, MRA showed activity in most patients seeming clinically in remission (49). Therefore, whether MRA can detect activity with only cross-sectional imaging. There are also efforts of MRA scoring systems aiming to assess cumulative vascular damage for the longitudinal follow-up TAK patients (49,50).

Positron Emission Tomography (PET)

Fluorodeoxyglucose (FDG)-PET imaging is based on the interpretation of FDG uptake by active inflammatory cells in vessel walls. It has become a widely used imaging tool for the diagnosis of LVV with high diagnostic sensitivity (>80%) (51). During semiquantitative analysis of PET images, 18F-FDG uptake of a vascular region of interest was compared with that of the liver [0= no uptake present, I= low-grade uptake (uptake present but lower than liver uptake), II= intermediate-grade uptake (similar to liver uptake), and III= high-grade uptake (uptake higher than liver uptake)] (52). Some studies also use the quantified 18F-FDG uptake such as standard uptake value (52,53).

A new scoring system, PET vascular activity score (PETVAS), was recently developed by Grayson et al. (54) The authors reported that PETVAS has a sensitivity and specificity of more than 80%. The total PETVAS score is calculated from nine arteries, which are the most frequently involved arteries in LVV. However, 58% of the TAK patients categorized as inactive according to the NIH criteria had active FDG-PET-CT findings in this study. Furthermore, 17% of non-vasculitic patients in the comparator group had active vasculitic lesions (54).

While it was suggested that glucocorticoid treatment decrease the FDG uptake (55), we did not find any affect of glucocorticoid or immunosuppressive treatment on PETVAS scores (56). Increased FDG uptake in the vessel wall in patients with LVV seeming in clinical remission may be associated with subclinical vasculitis (57) or non-vasculitic situations such as vascular remodeling, hypoxia (58), atherosclerosis (59). These all can be differentiated with only histopathologically.

PET is a very expensive imaging tool. Also, interpretation of FDG-PET-CT requires experience. One of the other limitations is the lack of standardization for the duration between FDG

administration and LVV acquisition. Radiation exposure during PET-CT imaging limits the use for follow-up of TAK patients (60). Promising results with PET-MRA showed that it is comparable with PET-CT. PET-MRA has better soft tissue resolution and anatomic definition and lower total radiation doses (61).

There are ongoing efforts focusing on the value of PET-MR on clinical activity assessment and treatment effects.

New ligand options in PET are also being assessed. Although promising results both in the diagnosis and activity assessment, PET is still not a standardized imaging method in TAK, especially for long-term follow-up of TAK patients.

Ultrasonography

US is a cheap and widely accessible imaging tool, and it can also be safely repeated during longitudinal follow-up. However, visualizing the aorta and subclavian arteries is difficult by US, with poorer detection of lesions. Carotid artery involvement can be visualized well with a high sensitivity (90%) and specificity (91%) in detecting stenotic lesions (62). Usage of mainly carotid, vertebral, subclavian, and axillary arteries and being an operator-dependent imaging modality are the main limitations of US during daily practice (63).

Treatment

Glucocorticoids are the mainstay of treatment for remission induction in TAK. The initial dose of prednisolone is 1 mg/kg/day (maximum 60 mg/day). The initial high dose should be maintained for a month and tapered gradually (1,20). According to the 2018 update of the EULAR recommendations for the management of LVV it was recommended that in patients who have reached 15-20 mg daily GC dose after 2-3 months, GCs should be decreased slowly targeting ≤10 mg/day at the end of one year (31). However, ≤10 mg/day doses of GCs in long-term remission are possibly too high compared with the recommendations in other disorders such as rheumatoid arthritis (usually ≤5 mg/day) and should be individually assessed in each patient according to the risk of GC-associated complications. Recent ACR guideline conditionally recommend tapering off glucocorticoids over long-term treatment with low-dose glucocorticoids for remission maintenance in TAK patients achieved remission while receiving GCs for ≥6-12 months (64). Both EULAR and ACR recommend the use of non-biologic disease-modifying agents in addition to glucocorticoids in all patients with TAK.

There are very low quality data coming from observational studies and case series showing the efficacy and safety of metotrexate (MTX), azathiopurine (AZA), mycophenolate mofetil (MMF), leflunomide (LEF), cyclophosphamide (CYC) in TAK treatment (1,22,65). Two open prospective series from China reported better outcomes with LEF than with CYC (66,67). Tacrolimus (68,69) and cyclosporine (70,71), which are calcineurin inhibitors widely used in transplant patients, were reported to be effective in very few cases with TAK. Tofacitinib compared with MTX and LEF in an open prospective series in TAK was found to be superior to LEF preventing relapse and decreasing the GC dose (72,73). There are only 2 double-blind RCTs on TAK treatment. Abatacept and tocilizumab (TCZ) failed in these studies when compared with plasebo (74,75). Long-term results of TCZ RCT study reported angiographic stabilization in patients (76). A recent open RCT reported similar clinical responses and angiographic stabilization in TAK patients treated with mycophenolate or methotrexate (29).

Several case series and observational studies reported the efficacy and safety of TNF inhibitors (TNFi) and TCZ in TAK (13,22). Two large retrospective comparison studies found similar clinical response rates and radiologic progression between TNFi or TCZ (77,78). A recent meta-analysis also confirmed similar clinical response, angiographic stabilization, and adverse events with TNFi or TCZ (79). In a head-to-head retrospective comparison, the drug survival rate of TNF was significantly higher than that of TCZ (67.2% vs 41.1%, p=0.028). Concomitant conventional immunosuppressive drug usage at baseline had a positive effect on the drug survival rate [HR = 3.79, 95% confidence interval (CI) = 1.49-9.60, p=0.005] (80). A retrospective, longitudinal follow-up cohort from Norway reported less angiographic progression at 2 years in patients with TAK receiving TNFi (10%) than in those receiving conventional immunosuppressive (40%). In this study, the angiographic progression rate was 90% in patients receiving glucocorticoid treatment only (81). According to EULAR recommendations, TCZ or TNFi can be equally considered in refractory patients (31). However, recent ACR guidelines recommend adding a TNFi over TCZ in refractory patients (64). A very recent open prospective study compared secukinumab and TNFi in patients with refractory TAK secucinumab and TNFi were found to be comparable regarding response rates at 3 and 6 months (82).

There are conflicting results with rituximab therapy in refractory TAK (83-85). Therefore, this limited experience of rituximab do not support a role for rituximab as the first or second line biologic therapy in TAK patients. There are case reports showing the efficacy of ustekinumab and anakinra in rafractory TAK patients (22,77,80,86,87). A phase 3 multicenter randomized control trial comparing upadacitinib vs placebo in TAK is currently active (https://clinicaltrials.gov/ct2/show/NCT04161898).

Vascular Interventions and Surgical Therapy

Except in emergency conditions, open or endovascular vascular interventions should be considered as the last option in case of medical treatment failure to prevent ischemic arterial symptoms or injury in TAK. As a general rule, such interventions should be avoided during the active phase of the disease and should be attempted only after suppression of vascular inflammation by appropriate IS treatment (88). According to data from case series, the main indications for surgery are as follows: refractory hypertension related to renal artery stenosis, aortic disease including coarctation and ascending aortic dilatation ± aortic valve regurgitation, ischemic heart disease, supra-aortic disease with cerebral ischemicemia, mesenteric ischemicemia, severe limb-threatening claudication, and aneurysm repair (89-93). In a recent meta-analysis comparing balloon angioplasty and stenting outcomes, there were no significant differences in the incidence of restenosis and other complications overall ($p=0.38$), but restenosis risk in stenting was significantly higher than that in balloon angioplasty (odds ratio = 4.40, 95% CI=2.14-9.02, $p<0.001$) in renal stenosis (94).

CONCLUSION

TAK is a rare systemic vasculitis mainly seen in young females. In the presence of typical symptoms and physical findings such as loss of pulses and/or decreased arterial blood pressure and elevated acute phase responses, the diagnosis should be confirmed easily by angiographic imaging modalities. Currently, conventional angiography is no longer considered as the "gold standard" imaging tool for the diagnosis of TAK. MRA is the gold standard modality for both the diagnosis and longitudinal follow-up of patients with TAK. Compared with DSA, three-dimensional MRA can effectively show vessel wall thickening, whereas contrast-enhanced MRA allows better soft tissue differentiation for assessing disease activity. In recent years, PET has become a widely used imaging tool for the diagnosis of TAK with high sensitivity. The place of PET during follow-up in TAK is still controversial and requires further studies. Prognosis is recently possibly getting better with lower mortality, but substantial damage is present even in early cases. It is critical to differentiate irreversible damage from disease activity and thus avoid potential overtreatment with toxic agents such as corticosteroids in TAK. There is a clear need to develop a validated set of outcome measures for use in clinical trials of TAK. In daily practice, routine imaging follow-up is not recommended in clinically and laboratory silent TAK patients assessed as inactive by the physician. The level of evidence for TAK management is low, and expert opinion is still the main determinant when managing patients with TAK during daily practice. Glucorticoids are the mainstay of TAK treatment. While tapering glucocoticoids, non-biologic immunosuppressive agents should be added to the treatment. LEF, MTX, AZA, or MMF could be chosen as the first -line immunosuppressive agents. If there is a treatment failure with first-line agents, switching to TNFi or TCZ should be considered. Despite an equal recommendation by EULAR recommendations after GCs plus IS failure in TAK, both ACR guidelines and our approach in our vasculitis clinic recommend a TNFi as the first-line biological due to a larger experience with TNFi.

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