**Update on Takayasu's arteritis**

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**Summary**

Takayasu arteritis (TAK) is a rare, chronic large-vessel vasculitis (LVV) that predominantly affects aorta, its major branches and the pulmonary arteries. Recent advances in the genetics, clinical course, prognosis, disease assessment with biomarkers/imaging/new scoring systems and new treatment options in TAK are discussed in this review. New imaging modalities such as MR angiography (MRA) and 18-FDG-PET seem to have replaced conventional angiography for the initial diagnosis in recent years. MRA and 18-FDG-PET are also promising for the assessment of disease activity. New tools for disease assessment such as Indian Takayasu Arteritis Score (ITAS2010) and colour-Doppler ultrasonography score (CDUS) aim to quantify disease activity better, however different imaging modalities, used in routine follow-up, are not sufficiently incorporated in these scoring systems. Prognosis is possibly getting better with lower mortality in recent years, however there are still widely different vascular intervention rates in clinical series. Leflunomide, TNF-α antagonists and tocilizumab are new options in patients resistant to conventional therapies.

Mikito Takayasu, a professor of ophthalmology at Kanazawa University, Japan, first described Takayasu's arteritis (TAK) as a case of retinal vasculitis with pulselessness in 1908 [1]. TAK is a chronic, large-vessel vasculitis (LVV) with a granulomatous histology, occurring predominantly in females in the second or third decades of life [2]. Most frequently involved large arteries are ascending/descending aorta, subclavian and extra-cranial arteries such as carotids (60–90%). Although the disease is observed worldwide, genetic factors associated with ethnicity are clear with most of the patients reported from East Asian countries including Japan, India, Korea and also recently from Middle-East, especially Turkey [3]. The disease generally has an indolent early course with constitutional features (fever, malaise, anorexia and weight-loss), extremity pain/claudication and light-headedness. Absent or diminished pulses, loss of blood pressure and bruits are characteristic and present according to the vessel involvement [4]. Although prognosis is improved in a recent Japanese series [5], there is still a significant delay in the diagnosis and mortality is...
increased [6,7], with a high rate of new, severe manifestations after diagnosis [8]. Vascular interventions are frequently performed to provide vascular patency, however their follow-up demonstrates a high incidence of thrombosis [9,10].

Genetics

Genetic studies demonstrated HLA-B*52, and to a lesser extent B*67 in Japan, as the most important HLA alleles associated with TAK in different ethnicities [11–13]. The role of fine epitope specificities of HLA alleles in pathogenesis is highlighted by the fact that HLA-B*51 and B*52, with only two amino acid differences in antigen-binding groove, are associated with completely different diseases: B*51 with Behcet's disease as an autoimmune inflammatory disorder, B*52 with TAK of a granulomatous nature [14,15]. Recently, the first two genome-wide association studies (GWAS) in patients from Turkey/USA and Japan confirmed another single nucleotide polymorphism association of TAK with IL-12B [16] and demonstrated a new one as FCGR2A/3A [17,18].

Classification

A set of classification criteria for TAK was established by the American College of Rheumatology (ACR) in 1990 [19] and criteria defined by Ishikawa et al. is also used in Japan [20]. Although ACR criteria have not been criticized as much as other criteria sets for small-vessel vasculitis (SVV) with over 90% sensitivity and specificity, the control group formed mainly of other SVV, which have limited overlapping vascular and clinical features with TAK. Therefore, usefulness of this criteria may be limited in real-life setting to differentiate TAK from giant-cell arteritis (GCA), atherosclerosis, congenital aortic vessel disease and the new entity IgG4-related disease [21,22]. To overcome these problems, a global Project, Diagnostic and Classification in Vasculitis Study (DCVAS) is underway to form new classification criteria for all vasculitides [23].

Prevalence and ethnicity

According to Japanese nation-wide registry, there were at least 5881 TAK patients in Japan in 2011 and the prevalence is thought to be > 0.004%. A systematic review collected only 197 patients from 7 Arab countries with a population of approximately 80 million, demonstrating a low prevalence [24]. The demographical and clinical findings of TAK in Arabs is reported to be similar to other series, with the course of the disease “quite stable” in about 50% of patients and the overall mortality is low during 5.4 years of follow-up. In a comparative study from France investigating TAK among white, North African and black patients, median age at diagnosis was 39.3 years in white, 28.4 years in North African and 28.0 years in black patients [25]. North African patients had more frequent relapses of ischemic strokes and poorer survival than whites. The 5- and 10-year survival rates were 100% and 95.0%, respectively, in whites; 100% at both 5 and 10 years in blacks and only 67.4% at both 5 and 10 years in North African patients, suggesting major differences in prognosis according to ethnicity.

Clinical course

New clinical series published recently better characterized the natural course of TAK. Grayson et al. demonstrated that among 6 different vasculitides, TAK has the highest rate of new, severe manifestation (ischemic, vascular) incidence (44%) [8]. Clinical features of “vascular symmetry” in TAK are investigated in 2 separate studies from USA and France [26,27]. Cluster analysis revealed that TAK lesions mostly develop in a symmetric manner in paired vascular territories and disease extension is continuous in the aorta. A similar observation is also present for GCA [26]. Computer-derived classification models showed that 56% of patients were classified into a subgroup that did not strongly differentiate between TAK and GCA. A high incidence of stroke development concomitant with the diagnosis of TAK is observed in Portugal [28]. Male gender represented an independent risk factor for the occurrence of abdominal pain and ascending aortic aneurysms in another cohort [29].

In a childhood TAK series with a median age-of onset of 12.5 years from India, most common presenting features were hypertension, headache and fever [7]. Majority of cases were active with increased acute-phase response (APR) and high activity scores. Although short-term remission was observed in most patients, only 29% were in sustained remission in 5 years. With aggressive medical and surgical intervention, the disease is stabilized in most patients. Another pediatric series of 71 patients is also reported from Brazil with 50% children (< 10 years old) [30]. Although clinical and angiographic data was similar between children and adolescents (10-20 years old), children had more anemia and thrombocytosis.

As before, most large series are published from East Asian countries recently. In a series of 204 patients, active cases had a higher incidence of significant aortic valve regurgitation and pulmonary hypertension, and a higher level of NT-proBNP [31]. Active TAK patients had more frequent involvement of the ascending aorta, aortic arch and its main branches than the inactive group. In another large series from China, coronary artery involvement was 7.7% among 587 patients and 8 patients died in a follow-up of 5.8 years [32]. Among 180 patients from Korea, SIR of cancer was observed comparable with that of the general population in TAK (1.3), only the risk of myelodisplastic syndrome was significantly increased (51.3) [33]. Significantly higher maternal complications including pregnancy induced hypertension, preeclampsia, postpartum hemorrhage and preterm labor is observed among 29 pregnancies in India [34]. Neonatal outcome also showed increased incidence of intrauterine growth restriction and neonates requiring NICU admissions. A better prognosis is published from Japan among 26 pregnancies with only 2 cases with hypertension, five
abortion and 2 growth restriction among newborns [35]. In 84 pregnancies among 36 Turkish patients, pregnancy outcome was also favourable with no major complications [36].

**Prognosis**

In a limited number of series, mortality seems to range between 3–15% in TAK [4]. In one of the largest series with a long-follow-up from Mayo Clinic, USA, overall survival was much better compared to earlier series (97% at 10 and 86% at 15 years) [6]. However, mortality was still increased compared to the general population (SMR: 3.0). Disease phenotype and severity of disease expression due to ethnicity, differences in medical therapy (e.g., less frequent use of glucocorticoids and cytotoxic agents) and variations in access to surgical therapy may give rise to different mortality rates. Similarly, the rate of interventional procedures is widely discrepant among series. Arterial reconstruction and bypass grafting may be necessary in up to 70% of patients with TAK to reverse some of the complications of the disease, for example renovascular hypertension [37]. However, the rate of surgical therapy changes between 12–50% in different cohorts. The restenosis rate after bypass procedures is also widely variable between 5–31%. Percutaneous transluminal angioplasty/stenting has a higher restenosis rate than the former (12–71.4%) [9]. The restenosis rate was reduced when surgical treatment was performed during the inactive stage of the disease and under treatment with both glucocorticoids and immunosuppressive (IS) agents [10,38]. These data suggest that early immunosuppression and the choice of treatment might influence the different rates of outcome in the literature. Finally, Ohigashi et al. first showed a decrease in the mortality of TAK with a rate of only 2.8% during 2000–2010 follow-up period [5].

**Assessment of disease activity with new outcome tools**

The most commonly adopted approach for disease assessment in TAK is the simple definition of “active disease” originally used in a study from US National Institute of Health (NIH) as the presence of constitutional symptoms, new-bruits, elevated APRs or new angiographic features [39]. A literature search performed for TAK have shown that items in NIH series were preferred by most studies to define “active” disease [40]. The Birmingham Vasculitis Activity Score (BVAS) is a validated tool for small and medium-vessel vasculitis that records the evidence of active vasculitis, listing multiple manifestations of vasculitis arranged by organ systems [41]. As used extensively in therapeutic trials of ANCA-associated vasculitis (granulomatosis with polyangiitis and microscopic polyangiitis) and endorsed by OMERACT, BVAS might be an outcome tool for the studies of TAK [42,43]. However, the differences in organ involvement in small vs. large-vessel vasculitis is a major concern and BVAS use may lead to unnecessary organ evaluation for LVV, whereas cardiovascular findings may be under-investigated.

The Indian Takayasu Clinical Activity Score (ITAS2010) is the current major attempt to develop a disease activity score for TAK [44]. During the development stage of ITAS2010, a disease-extent index for TAK (DEI.Tak) with 71 items was created using BVAS as a template [45]. In the DEI.Tak, and later on in ITAS2010, items directly related to large arterial disease (e.g., stenosis and claudication) are weighted for scoring than general items of disease (e.g., fever, fatigue), aiming to give a more detailed perception of the cardiovascular findings. As a result of this approach, compared to BVAS which incorporates nearly all of the disease features that clinicians routinely use to evaluate disease activity, 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) [46]. ITAS2010 seems to have a good comprehensiveness and the inter-rater agreement seems better than physician’s global assessment (PGA) (0.97 vs. 0.82). However, convergent validity, when assessed by comparison to PGA, was quite low at the initial evaluation, improving only at subsequent visits (r = 0.51, 0.64, and 0.72). The authors made a further attempt to incorporate 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. Furthermore, when “response to change” was assessed by ITAS2010-A, patients still had a mean score of 4 at the third visit, when they were deemed to be clinically inactive with PGA. Presence of ITAS2010 items during apparent remission is problematic and illustrates the substantial difficulty in differentiating activity from damage due to non-vasculitis-related problems in this disease [46]. The suggestion to have a cut-off of 4 points to separate active and inactive disease states does not satisfactorily address this underlying limitation.

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 ITAS2010. However, the limitations of physical examination were recently shown in a study comparing physical signs with imaging data [47]. 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 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 ITAS2010 with PGA suggests that physicians might accept some patients as “active” with only increased APR or new abnormalities on vascular imaging studies. In a study of DEI.Tak, there was a disagreement in 49% of the assessments between DEI-Tak and PGA, showing that – although not being the gold standard – physicians tend to take into account the imaging findings as well as APRs and possibly not take all positive manifestations as a disease flare [45].

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Imaging in TAK

Imaging in TAK has relied on conventional angiography, which demonstrates mainly luminal blockage rather than vessel wall involvement [48,49]. Computerized tomography (CT) provides excellent anatomical characterization of structural aortic changes, but is limited in its assessment of early disease activity [50]. MR angiography can show vessel wall thickening and oedema, however this correlates poorly with clinical activity or APR and is shown to have a limited role for long-term follow-up [51-53]. 18-FDG-PET is the most sensitive test for early vessel inflammation, however, it requires CT or MR imaging for anatomic localization. Activity in 18-FDG-PET is suggested to demonstrate active or relapsing disease which decrease after immunosuppression [54-57]. A recent meta-analysis of 6 studies with 18-FDG-PET reported its sensitivity as 70.1% and specificity 77.2%, with a moderate diagnostic value [58]. In an expert panel study of 30 patients with LVV, 18-FDG-PET is concluded as a sensitive and specific imaging tool [59]. However, although widely interpreted as inflammation, 18-FDG-PET scans do not correlate sufficiently with symptoms or the pattern of stenosis/occlusion. As glucose uptake in 18-FDG-PET is not limited to inflammatory cells in vascular wall, hot 18-FDG-PET scans may also be observed in patients in clinical remission [60].

Ultrasonography (US) has the advantages of avoiding the high radiation dosage of angiography or 18-FDG-PET, and is cheaper and more widely available, particularly relevant in countries with less resources where TAK is more common [61]. A high rate of atherosclerotic plaques was shown previously with Carotid US in TAK [62]. Recently, Seyahi et al. combined US with multi-detector CT and detected a high prevalence of thoracic aorta calcifications [63]. Carotid contrast-enhanced US is also suggested as a better method for the visualization of the carotid lumen border, and may allow a dynamic assessment of carotid wall vascularization and intima-media thickening [64,65]. Sinha et al. recently presented a colour-Doppler ultra-sound imaging (CD.US) quantitative score for TAK [66]. The score includes 19 vascular regions, scoring each for both stenosis and flow pattern, reflecting the vessels where pulse loss can be detected clinically in TAK. Intra-thoracic vessels such as the commonly involved subclavian are difficult to visualize by CD.US and produced the lowest kappa values in this study. CDUS.K scores each vessel dichotomously (as 0 and 1), thus limiting the assessment of further changes in the vessel lumen. This can be a serious issue when clinical signs or APR point to a “new” relapse, and the physician might have to turn to conventional imaging for sensitive assessment of the vessel changes. Serial assessments compared to angiography and clinical features are essential to clarify these issues [61].

Subclinical cardiac and pulmonary disease is also studied in TAK with highly sensitive imaging modalities such as myocardial scintigraphy, cardiac magnetic resonance imaging with late gadolinium enhancement, dual source CT-angiography, 18-FDG-PET and pulmonary perfusion scintigraphy [67-72].

Biomarkers

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 [2]. Serum autoantibodies such as anti-endothelial antibodies, circulating endothelial cells and serum biomarkers such as VEGF, IL-6, IL-8, IL-18, matrix metalloproteinase-9 and adipokines are also investigated [73-78]. Recently Pentraxin3 (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 [79,80]. In a single center 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) [80]. In another study from Japan, among 28 patients with active TAK, 71% was positive for hsCRP and 82% for PTX3 [79]. However, these data require confirmatory studies to show whether PTX3 is superior to CRP.

Damage assessment and patient reported outcomes

One of the major difficulties in LVV is the differentiation between activity vs. damage. A vascular stenosis may be due to the inflammation if it is taking place in an acute phase- elevated state, however may also be a sign of an ongoing narrowing of the vessel wall in longstanding disease. The role of atherosclerosis in this process is also not clarified. Damage is not a well-studied domain in LVV, with also a not fully-published, new instrument from India [7,81]. Further research is needed to test the discriminatory capacity of the clinical findings such as systemic inflammation and vascular insufficiency in differentiating activity and damage [82].

Currently there are no disease specific outcome tools to assess patients’ perspective in LVV. General instruments, like SF-36 and hospital anxiety and depression scales have been tested in TAK and found to be impaired [83-85]. Fibromyalgia (FM), although not increased compared to controls, seem to be associated with active disease in TAK and FM subscales are impaired in patients with lower QoL, anxiety and depression scores [86].

Treatment

Like in all orphan diseases, the rarity of TAK is a major limitation for randomized controlled trials (RCT) and, except an ongoing one, there are no RCTs published in TAK [40,87]. Therefore, treatment choices are mainly determined by observational studies and the clinicians’ decision based on expert opinion.
This lack of studies can partly be explained with the low incidence [13], and unlike SVV, lack of international collaborative studies. This is reflected in EULAR guidelines for the management, where, except IS use, all recommendations have an evidence level of 3 and strength of C [87-89]. However, recent uncontrolled data of leflunomide, TNF-α-antagonists and tocilizumab in refractory TAK seems promising. Leflunomide is shown to be effective in a short-term study of 14 TAK patients with active disease despite therapy with corticosteroids and IS agents. In this study, activity decreased with leflunomide (93% to 20%), mean daily dose of prednisone (34.2 to 13.9 mg) lowered and the median values of ESR and CRP fell [90]. Among biological agents, tocilizumab is currently the mostly popular one, studied in 9 case-series and some individual cases in the last five years [81,91-95]. A recent literature review summarizes 44 cases in 2013, with a mean follow-up of 9 months [96]. At the last visit, tocilizumab was continued in 53% and was discontinued in the 15 remaining cases because of remission (n = 5), relapse (n = 3), persistent radiological activity (n = 3), cutaneous rash (n = 2) and severe infection (n = 1). As sustained remission could only be achieved with long-term treatment in most patients, different biological agents might be required during long-term follow-up. Whether these biologic agents should be considered earlier in the treatment algorithm of these complicated patients remains an area of interest.

**Conclusion**

Although outcome measures are not clearly validated, progress in the assessment of Takayasu's arteritis is reflected in recent studies when clinical, acute-phase response and serial non-invasive imaging is shown to reflect a good prognosis in patients treated with biological agents with no long-term increase in damage [81,97]. Recent progress in management also requires better disease assessment tools for clinical studies [87].

**Complementary references**

Three important new papers have been published since the review was written, please refer to [98-100].

**Disclosure of interest:** the authors declare that they have no conflicts of interest concerning this article.

References


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