

## Takayasu arteritis: an update

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**Abstract:** Takayasu arteritis (TAK) is a challenging chronic, granulomatous, large-vessel systemic vasculitis, mostly due to difficulties in early diagnosis and assessing actual disease activity. Since there are no specific diagnostic laboratory tests, biomarkers, or autoantibodies, many patients experience considerable delay in diagnosis. Remembering the possibility of TAK together with the use of acute phase responses and appropriate imaging studies may be helpful for early diagnosis. Since there may be discrepancies between systemic and vascular wall inflammation, using only acute phase responses is not reliable in assessing current disease activity. Therefore, physical examination and new imaging findings should also be used to assess current disease activity. Despite its limitations, the Indian Takayasu Clinical Activity Score (ITAS2010) may also be helpful for this purpose. The rationale of medical treatment is to suppress both vascular and systemic inflammation with appropriate systemic immunosuppression, including corticosteroids and conventional immunosuppressive agents. In cases of refractory disease activity, leflunomide and biologic agents such as TNF inhibitors and tocilizumab may be tried. In selected cases with persistent lesions that cannot be reversed with medical treatment, endovascular interventions including balloon angioplasty, stent and stent graft replacement, or surgery may be tried. However, such procedures should be performed after suppression of inflammation, i.e. during inactive disease. Prognosis of TAK is probably getting better with lower mortality rates reported in recent years, probably due to the use of more effective medical treatments as well as the use of endovascular interventions when necessary and available.

**Key words:** Takayasu arteritis, large vessel vasculitis, management, diagnosis, disease activity

### 1. Introduction

Definition, basic concepts, and epidemiology of Takayasu arteritis Takayasu arteritis (TAK), also known as “pulseless disease”, “aortic arch syndrome”, or “occlusive thromboarthropathy”, was first described by Mikito Takayasu, a professor of ophthalmology at Kanazawa University in Japan, as a case of retinal vasculitis with pulselessness in 1908 (1). TAK is a chronic, granulomatous, large-vessel vasculitis, characterized by stenosis, occlusion, and sometimes aneurysm of the aorta and its main branches, especially of the subclavian, common, and internal carotid arteries. However, other large vessels including pulmonary arteries, as well as medium-sized coronary arteries, may also be involved (2,3). The clinical picture varies based on the arteries involved and the severity of inflammation. TAK generally follows an insidious course at onset, but presentation with atypical and/or catastrophic disease, such as with acute visual loss or stroke, may also occur (4,5). Unfortunately many patients experience considerable delay in diagnosis since there are no specific diagnostic laboratory tests, biomarkers, or autoantibodies (2,6).

TAK occurs more commonly in young females, generally in those less than 40 years of age, although it may also be seen in older patients (7). TAK is present more often in Far Eastern and Asian countries, while it is relatively uncommon in northern European and American countries (7,8). Ethnicity is an important factor not only for the frequency of TAK, but also for the severity and the prognosis of the disease. While a Japanese nation-wide registry reported at least 5881 TAK patients in Japan in 2011 with a prevalence higher than 4/million (8), only 197 patients from seven Arab countries with a total population of approximately 80 million could be enrolled in a recent study (9). In a population-based study performed in the United Kingdom, Watts et al. found that the overall annual incidence of TAK was 0.8/million, while the mean prevalence was 4.7/million (7).

In Turkey, it is presumed to be the second most frequent systemic vasculitis seen in the adult population, after Behçet's disease. Recently, Birlik et al. investigated the prevalence and incidence of TAK among the residents of the city of İzmir, which is the third largest metropolis

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in Turkey, located in the Aegean region (10). The annual prevalence was estimated as 12.8/million in the total population and 23.5/million in females. The prevalence was higher than 8.8/million in the population >40 years of age. During the study period, the mean annual incidence of TAK was estimated as 1.11/million (10). In another study conducted in the northwestern part of Turkey, the annual incidence rate for TAK was found to be 0.34/100,000, while the overall prevalence was 3.3/100,000 in individuals >16 years of age. The authors concluded that in the northwestern part of Turkey the annual incidence and prevalence of TAK were higher than in the western population, but similar to East Asian data (11).

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 (12). 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 (12).

## 2. Clinical features of Takayasu arteritis

Generally three different phases of TAK are recognized. In the first phase, there are nonspecific constitutional inflammatory symptoms. During this phase, TAK may even present as fever of unknown origin. In the second phase, mural inflammation starts in the large arteries, causing carotidynia perceived as neck pain and sometimes additional thoracic and dorsal pain. The third phase represents the late phase, characterized with decreased or absence of pulses and/or differences in arterial blood pressure between upper extremities, arterial bruits, and intermittent extremity claudication. The complete form of TAK may also be divided into two overlapping phases. While the acute phase represents systemic and initial vascular inflammation, the occlusive phase, which occurs weeks to years later, is characterized by ischemic symptoms (4,13–15). During the course of TAK, occurrence of new, severe ischemic, vascular manifestations is quite common compared to other systemic vasculitides, as reported by Grayson et al. (16). Severe hypertension in TAK may be caused by atypical coarctation of the aorta, loss of vascular compliance, aortic valve regurgitation due to aortitis, or renal artery stenosis. Stroke, transient ischemic attack, and sudden blindness may also be caused by thrombosis of cerebral arteries (13–15,17). Erythema nodosum is reported as the most common skin lesion in TAK in Caucasian populations (17,18).

Although involvement of the aorta and its main branches is part of the definition of TAK, it should be

noted that this involvement is not homogeneous in all patients with TAK. Rather, there are different types of involvement, and initial clinical findings may be different based on the location and extent of vessel involvement. The most widely used classification of TAK is based on conventional angiographic findings, as reported at the International Conference on TAK in 1994. According to this classification there are six different types of vessel involvement in TAK (19):

- Type I involves the branches of the aortic arch;
- Type IIa involves the ascending aorta, aortic arch, and branches of the aortic arch;
- Type IIb involves the thoracic descending aorta with the involvement of Type IIa;
- Type III involves the thoracic descending aorta, abdominal aorta, and/or renal arteries;
- Type IV involves the abdominal aorta and/or renal arteries;
- Type V is the combination of Type IIb and Type IV.

## 3. Diagnosis of Takayasu arteritis

Currently there are no universally accepted diagnostic criteria for systemic vasculitides, including TAK. Rather, there are classification criteria, originally defined to classify patients who were already diagnosed with vasculitis, for including these cases in certain clinical trials (20). The most widely used vasculitis classification criteria are the American College of Rheumatology (ACR) criteria, which were defined in 1990 (21). The ACR criteria for TAK consist of: 1) age of onset before 40 years old; 2) claudication of an extremity; 3) decreased brachial artery pulse; 4) a difference of more than 10 mmHg systolic pressure between two limbs; 5) a bruit over subclavian arteries or the aorta; and 6) angiographic evidence of narrowing or occlusion of the aorta, its primary branches, or large arteries in the proximal upper or lower extremities. The presence of three of the six criteria is required for differentiating TAK from other systemic vasculitis.

There is also another set of diagnostic criteria (20) for TAK, proposed by the Japanese Research Committee on Vasculitis Syndromes, which include: 1) angiographic evidence of narrowing or occlusion of the aorta, its primary branches, or large arteries in the proximal upper or lower extremities by digital subtraction angiography (DSA), CT, or MRI; 2) early age of onset; 3) presence of markers of inflammation; and 4) exclusion of patients with atherosclerosis, inflammatory abdominal aortic aneurysm, vascular Behçet's syndrome, syphilitic aortitis, giant cell arteritis (GCA), congenital vascular abnormality, and mycotic aneurysm.

Unfortunately the ACR 1990 criteria generally cover cases of TAK in the late stage, where it is not difficult to make the diagnosis. In the context of typical clinical

symptoms and physical findings such as loss of pulses and/or decreased arterial blood pressure, and elevated acute phase responses, various vascular imaging methods may easily confirm the diagnosis of TAK. In the ACR 1990 criteria for TAK, the only vascular imaging modality included is conventional radiographic angiography or DSA (21).

Early diagnosis of TAK in the first or second stages is the real goal, but difficult to establish. Firstly, the clinician should remember the possibility of this disease in suspected cases. There are nine red flags that may alert a clinician to investigate TAK in a young patient with unexplained systemic inflammation, as shown in Table 1 (6). In our opinion, erythema nodosum may also be included among those red flags.

Another point to be considered in the early diagnosis of TAK is that initial clinical findings may be different in different types of TAK. For example, involvement of renal arteries is prominent in type IV TAK, which may lead to the presence of HT more frequently and as an early finding. Type IV is seen more commonly in India and other South Asian countries; therefore, recent onset of HT in the presence of systemic inflammation may implicate a possible diagnosis of TAK in those countries (22).

Whenever the possibility of TAK comes to the mind of the clinician, the diagnosis of TAK should be confirmed by the imaging methods discussed and compared with each other in the following section. Overall, narrowing or occlusion of the aortic arch and proximal parts of its branches is highly suggestive of the late stages of TAK. Involvements of subclavian arteries, especially the left side, and of common/internal carotid arteries are typical for TAK. Cluster analysis also revealed that TAK lesions mostly develop in a symmetric manner in paired vascular territories and disease extension is contiguous in the aorta (3,23).

### 3.1. Use of imaging methods in the diagnosis and follow-up of patients with Takayasu arteritis

DSA is a useful imaging method not only for the diagnosis but also for the assessment of the extent and localization

of vascular involvement in TAK. DSA may detect arterial stenoses, occlusions, and aneurysms in large and medium-sized vessels. However, DSA only visualizes the lumen of the vessel, without giving any information about the vessel wall. DSA may miss minor, nonocclusive lesions and also does not have adequate resolution for small vessels. Besides, it is an invasive method causing exposure to contrast media and radioactivity (24–26). It should be noted that DSA is no longer the gold standard for diagnosis of TAK (8,25,27).

Currently, many physicians prefer to use magnetic resonance angiography (MRA) or computerized tomography angiography (CTA) for establishing the diagnosis of TAK. MRA and CTA are helpful for the evaluation of the aorta and its primary branches. CTA may provide excellent anatomical characterization of structural changes in the aorta, but may not detect early disease activity (28). Although MRA can show vessel wall thickening, edema, and contrast enhancement, (29), it has been shown that correlation with clinical activity or systemic inflammation is poor and it is shown to have a limited role for long-term follow-up (30,31).

On the other hand, color Doppler ultrasonography (CDU) is helpful to evaluate temporal, carotid, axillary, and femoral arteries, but it fails to depict the thoracic aorta unless performed as a transesophageal examination. Similar to MRA and CTA, CDU can not only visualize luminal changes, stenoses, and aneurysms of large arteries; it can also detect the characteristic homogeneously thickened vessel walls, as well as mural inflammation and edema, which are early inflammatory signs. CDU also provides better resolution than MRA and CTA (26). There is no risk of radiation exposure in MRA and CDU. Disadvantages of MRA include overestimation of vascular occlusions and inability to visualize small branch vessels and vascular calcifications.

Positron emission tomography (PET) with 18F-fluorodeoxyglucose (18F-FDG PET) is a noninvasive imaging method that measures 18F-FDG, which accumulates in hypermetabolic, activated inflammatory cells infiltrating the vessels. On the other hand, 18F-FDG PET/CT combines the functional information from PET and the anatomical information from CT. 18-FDG-PET is the most sensitive test for early vessel inflammation. Therefore, both early vascular inflammation and its location in the aorta and its branches may be detected using PET-CT in the first two phases, which may help in the early diagnosis of TAK. However, vascular uptake on PET is not specific for vasculitis, and discriminating between atherosclerotic and vasculitic lesions may be challenging. Unfortunately, PET cannot delineate the vessel wall structure and luminal flow; besides, the radiation exposure is high, particularly in PET-CT (32–34). A metaanalysis

**Table 1.** Red flags to investigate Takayasu arteritis in a young patient with otherwise unexplained systemic inflammation.

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

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of six studies with 18-FDG-PET reported its sensitivity as 70.1% and specificity 77.2%, with a moderate diagnostic value (35).

In summary, MRA, CTA, CDU, or in selected cases 18F-FDG PET-CT may be helpful in the early diagnosis of TAK, before the narrowing of the vessel lumen; unfortunately, this is not possible with DSA.

#### 4. Genetics of Takayasu arteritis

Although the etiology of TAK is still unknown, genetic factors clearly contribute to pathogenesis (36).

Some major progress in understanding the pathogenesis of TAK came with the first two genome-wide association studies (GWASs) from Turkey/the United States and Japan, demonstrating the role of HLA-B\*52 and single nucleotide polymorphism associations with IL-12B and FCGR2A/3A (37–39). FCYR2A/3A association is also shown in the Chinese population (40). Interestingly, IL-12B is also shown to be a common genetic component between GCA and TAK (41).

In the recent larger GWAS study, new genetic susceptibility loci for TAK with a genome-wide level of significance in the IL6 gene (odds ratio [OR] = 2.07), RPS9/LILRB3 (OR 1.65), and an intergenic locus on chromosome 21q22 (OR = 1.79) were also demonstrated (42). The genetic susceptibility locus in RPS9/LILRB3 lies within the leukocyte receptor complex gene cluster on chromosome 19q13.4, and the disease risk variant in this locus correlates with reduced expression of multiple genes including the inhibitory leukocyte immunoglobulin-like receptor gene LILRB3. In addition, other candidate susceptibility genes with suggestive levels of association with TAK, including PCSK5, LILRA3, PPM1G/NRBP1, and PTK2B, were also shown in this study. In the largest ever genetic study of different vasculitides including large and medium vessel types, the strongest association signal corresponded with an intergenic polymorphism located between HLA-DQB1 and HLA-DQA2 (OR = 0.74). This single nucleotide polymorphism is in moderate linkage disequilibrium with the disease-specific human leukocyte antigen (HLA) class II associations of each type of vasculitis and could mark them. Outside the HLA region, the KDM4C gene was identified as a common risk locus for vasculitides (OR = 1.75). This gene encodes a histone demethylase involved in the epigenetic control of gene expression (43).

#### 5. Immune pathogenesis of Takayasu arteritis

Other than genetic factors, infectious agents are also accepted to contribute to the pathogenesis of TAK (44). Whatever the exact triggering factors are, a cell-mediated immune response is triggered, as also suggested by histological findings showing inflammatory cell

infiltrations and necrosis of the arterial vascular wall (45–47). Vascular inflammation of TAK possibly originate in the vasa vasorum, followed by infiltration of inflammatory cells with the production of inflammatory and Th1-type cytokines, such as tumor necrosis factor (TNF)- $\alpha$ , interferon (IFN)- $\gamma$ , interleukin (IL)-12, and IL-18, leading to the formation of granulomas (48). Th17 cells induced by IL-6 and IL-23 in the microenvironment possibly also contribute to the vascular lesions through the recruitment of infiltrating neutrophils (49). IL-12/IFN- $\gamma$ -associated Th1 and IL-6-IL-17 and IL-23-dependent Th17 pathways are more clearly defined in GCA, a similar large vessel vasculitis. In recent studies, increased B-cell aggregates are also shown in the adventitia of the aorta in TAK patients, suggesting that B-cell depletion therapy might also have value in treatment (50,51).

In a search to find better biomarkers for disease assessment, in various previous studies, serum concentrations of IL-6, RANTES (regulated on activation, normal T cell expressed and secreted), IL-8, IL-12, and IL-18 were studied and some appear to correlate with disease activity (52–56). Matrix metalloproteinase-9 and recently pentraxin3 (PTX-3) have also been suggested to be related to active disease in TAK; however, these data require confirmatory studies (57,58).

IL-6 is a proinflammatory cytokine mainly synthesized by activated monocytes, macrophages, and T cells and has an important role in the Th17 pathway. Serum IL-6 levels have been shown to be raised in active GCA and TAK patients, correlating with disease activity (59). IL-6 receptor blockage also seems to be the most promising new treatment option for large vessel vasculitides. IL-23 is a member of the IL-12 family, which is important for the generation and maintenance of Th17 cells. IL-23 has been associated with the generation of a particularly proinflammatory subset of Th17 that expresses both IL-17 and IFN- $\gamma$ . Serum IL-23 levels were similar to those of healthy controls in patients with TAK. However, IL-23 levels stayed high in inactive disease, suggesting that it might be a factor for disease relapses, similar to the observations in GCA (58,60).

Antiendothelial cell antibodies and the mammalian target of rapamycin (mTOR) pathway were also reported to contribute to vascular inflammation in TAK. Higher levels of serum antiendothelial cell antibodies were detected in TAK patients compared to controls. The activation of both mTORC1 and mTORC2 specifically in endothelial cells from TAK patients was also shown (61,62).

#### 6. Systemic inflammation versus vascular wall inflammation in Takayasu arteritis

Systemic inflammatory response does not always show a positive correlation with inflammatory activity in the



vessel wall. Therefore, TAK may be active despite normal erythrocyte sedimentation rate (ESR) and serum CRP levels, and vice versa (63). In patients with apparent clinical and laboratory remission, arterial specimens may show histological signs of vasculitis (4,63). Recently it has been shown that there are clear discrepancies between these two types of inflammation, including cytokine patterns and even responses to treatment. Although no definite boundaries exist, it may be suggested that the IL-6/Th17/IL-17 pathway primarily drives systemic inflammation, while the IL-12/Th1/IFN- $\gamma$  pathway dominates in vascular wall inflammation not only in TAK but also in GCA (48,64). Corticosteroid (CS) and immunosuppressive (IS) treatments initially suppress systemic inflammation, while longer treatment duration is required for the suppression of vascular inflammation. Therefore, evaluating only the systemic inflammation may be misleading. Vascular wall inflammation is currently evaluated using expensive imaging methods that are not feasible for repetitive use. Although PTX-3 is superior to ESR and CRP, we need more reliable biomarkers to reflect vascular wall inflammation in patients with TAK. However, identifying these biomarkers is very challenging and may be accomplished only by means of prospective, multicenter studies utilizing repetitive imaging together with serial serum samples for biomarker studies in a cohort of newly diagnosed TAK patients (48).

### 7. Assessing disease activity in Takayasu arteritis

Due to the discordance between systemic and vascular wall inflammation in TAK, in clinical practice, suppression of vascular inflammation is generally evaluated by imaging methods, especially MRA. On the other hand, monitoring overall disease activity in TAK may be accomplished by the integrated use of noninvasive imaging methods, patient symptoms, clinical findings, and acute phase reactants (27). There is no single imaging modality that can provide all the information required and each method has distinct and complementary roles in monitoring (25).

To identify effective new biomarkers, we need inflammatory molecules that are locally produced at sites of vascular inflammation, which are expected to better reflect the degree of vascular wall inflammation. Since PTX-3 is involved in the maintenance of vascular homeostasis (65), measuring plasma levels of PTX-3 was suggested as a more reliable and promising biomarker to reflect vascular disease activity in TAK (58,66,67). Tombetti et al. showed that PTX-3 may identify vascular progression only in a subgroup of TAK patients not receiving anticytokine treatments, while levels of CRP more accurately reflected the burden of systemic inflammation. However, in other patients with TAK, including those receiving anticytokine treatments, even plasma PTX-3 levels were shown to be

normal despite ongoing smoldering vascular inflammation (66). In other words, although PTX-3 certainly had some advantages compared to CRP, it unfortunately could not solve the problem of detecting smoldering vascular wall inflammation in TAK.

In the literature, there are criteria defined for assessing disease activity in TAK. According to the Kerr criteria (4), the presence of recent occurrence or deterioration of at least two of the following four criteria shows active disease: 1) systemic features like fever and arthralgia that cannot be explained by other reasons; 2) elevated ESR; 3) findings of vascular ischemia and inflammation; and 4) typical angiographic findings.

The Disease Extent Index Takayasu (DEI.Tak) was defined in 2005 for the follow-up of TAK by assessing only new clinical findings within the past 6 months without a requirement for imaging techniques or acute phase reactants (68). DEI.Tak was created using BVAS as a template and included 71 items. The items directly related to large arterial disease including stenosis and claudication were weighted for scoring more than general items of disease (e.g., fever, fatigue), aiming to give more importance to cardiovascular findings. The DEI.Tak was shown to be a practical and valuable tool to assess disease activity and progression in a Turkish TAK series (69). Recently, the Indian Takayasu Clinical Activity Score (ITAS2010) was published as a disease activity score for TAK (70). The ITAS2010 has only six systems and, similar to DEI.Tak, scoring was also weighted for vascular items. The ITAS2010 only evaluates the clinical features of the disease occurring during the prior 3 months, assessed by a physician; however, evidence of blocked vessels documented by vascular imaging for determining pulse losses is also included (8,70,71). The ITAS2010 seems to have a good comprehensiveness and the interrater agreement seems better than a physician's global assessment (PGA) (0.97 vs. 0.82) (8). Misra et al. also made a further attempt to incorporate acute phase responses into the score by adding an extra 1–3 points for elevated ESR or CRP, thus creating the ITAS2010-A. However, ITAS2010-A scores were found to be higher both in active and inactive patients. In other words, ITAS2010-A scores may remain high even in patients responding to treatment and being accepted as clinically inactive according to the PGA. Although the authors suggested an ITAS2010 score of 4 points as a cut-off to separate active and inactive disease, the presence of ITAS2010 items during apparent remission is an important problem, and there is substantial difficulty in differentiating current TAK activity from damage due to problems not related to vasculitis (8). Physical examination for new vascular signs was accepted as the major tool in the ITAS2010. However, there are also limitations of physical examination, as recently shown by

Grayson et al. (72). The authors compared physical signs with imaging data and reported that individual physical examination findings had poor sensitivity (14%–50%) and at least 30% of the lesions detected by imaging were missed. Therefore, clinical assessment should be combined with acute phase responses and new imaging findings to assess current disease activity.

### 8. Similarities and differences between Takayasu arteritis and giant cell arteritis

There is an ongoing debate concerning whether TAK and GCA may represent a spectrum of the same disease (64,73,74). Similarities of these two diseases may be summarized as the common role of cell-mediated immunity in their pathogenesis, similar pathological findings in the vessel wall, and high serum levels and vascular expressions of certain cytokines including IL-6 and IL-17. Recently, a metachip analysis including both GCA and TAK patients revealed IL-12B as the most prominent genetic factor for both diseases (41).

On the other hand, there are striking differences between GCA and TAK, including age of onset, ethnic discrimination, clinical features, and vascular distribution. While TAK is generally seen in young females from Far Eastern and Asian countries, GCA is generally seen in older patients especially of Caucasian origin. Unlike TAK, which tends to affect branches of the internal carotid artery, GCA has a tendency to affect branches of the external carotid artery. Therefore, headache, jaw or tongue claudication, and scalp tenderness are not expected to occur in TAK, unlike stroke, which is more common in TAK compared to GCA. Although involvement of the aorta and its main branches is more typical for TAK, it should be noted that there is a subgroup of GCA presenting in this way, without cranial arteritis, as discussed above (64,73,74).

Grayson et al. investigated the distribution of arterial lesions in two North American cohorts consisting of 145 patients with TAK and 62 patients with GCA (3). Cluster analysis demonstrated that arterial involvement was contiguous in the aorta and usually symmetric in paired branch vessels both for TAK and GCA. They reported that carotid and mesenteric arterial diseases were seen more frequently in TAK, and axillary disease was more frequent in GCA. While subclavian involvement tended to be asymmetric in TAK with a high frequency of left subclavian artery disease, symmetric subclavian with concomitant axillary involvement was seen more frequently in GCA. However, cluster analysis of arterial involvement could not show differences between TAK and GCA in 56% of patients. Given that there are strong similarities but also subtle differences in the distribution of arterial disease between TAK and GCA, these authors suggested that TAK and GCA might exist on a spectrum within the same disease (3).

The types of cytokines primarily suppressed by CS treatment, i.e. cytokine response patterns, are also different in TAK and GCA. In patients with TAK, serum levels of Th1 cytokines are easily suppressed, while Th17 cytokines are resistant (49,64). On the other hand, in patients with GCA, the Th17 pathway is rapidly suppressed, while the Th1 pathway (IFN- $\gamma$  production) is relatively CS-resistant and responsible for ongoing vascular inflammation (75,76). TNF inhibition may also be effective in the treatment of TAK (77,78), while it remains relatively ineffective in GCA (64,79).

### 9. Differential diagnosis between Takayasu arteritis and atherosclerosis

Various pathologies may cause narrowing of the lumen in the aorta and its branches. Among those mimickers, atherosclerosis is probably the most commonly encountered pathology, and differentiating atherosclerotic lesions from vasculitic lesions, especially in older patients with TAK, is not always easy. Furthermore, there is a well-known association between inflammation and atherosclerosis, which may result in the presence of both vasculitic and atherosclerotic lesions in TAK (80). Given that atherosclerosis is also an inflammatory process, atherosclerotic plaques may also cause increased uptake of gadolinium contrast in MRA and increased FDG uptake in PET-CT imaging, resulting in further confusion (81). Practical points helpful in differentiating these lesions include the following (80,82,83):

- Atherosclerotic lesions tend to be localized in bifurcation sites and in ostia in isolated atherosclerosis, while they are generally located on proximal parts of the arteries in TAK.
- Traditionally, atherosclerosis is a major risk factor especially for abdominal aortic aneurysms, while TAK may cause both thoracic and abdominal aortic aneurysms.
- The arteries of the upper limbs are rarely involved in atherosclerosis, which is helpful in differential diagnosis.
- Coronary calcifications are typical for atherosclerosis, rather than TAK.
- Atherosclerosis causes localized, nonhomogeneous, and irregular mural thickening, while TAK causes diffuse and homogeneous arterial vessel wall thickening.
- In PET-CT imaging, atherosclerotic lesions of the aorta are generally seen as localized hot spots, while vasculitic lesions may be seen as linear smooth PET signals.
- Using CDU, atherosclerotic lesions usually present with localized thickening of the intima-media complex, while the presence of dark hypoechoic circular vascular wall thickening around the femoral arterial lumen, the so-called halo or macaroni sign, suggests the diagnosis of vasculitis. Concentric, smooth thickening of the arterial vessel wall, leading to long-segment stenosis, is also typical for lower limb vasculitis.

- Using MRA, increased vessel wall thickness of the large arteries with linear mural contrast enhancement on T1 sequences and vessel wall edema on T2 sequences may suggest the diagnosis of vasculitis.

- Using CTA, calcifying plaques may be visualized, which can distinguish between atherosclerotic and inflammatory lesions.

- Punctate, linear calcifications and discrete plaque lesions and patchy involvement suggest atherosclerosis, whereas mural and circumferential calcifications with uniform and diffuse involvement suggest TAK.

## 10. Management of Takayasu arteritis

For optimum management of TAK, the pattern and extent of arterial involvement as well as current disease activity should be known. Patient education, cooperation between the doctor and the patient, and supportive measures should not be ignored. Although the rationale of the management is to suppress both vascular and systemic inflammation with medical treatment, endovascular interventions and/or surgical procedures may be also tried in selected cases with critical arterial stenosis. However, as a general rule, such interventions should be avoided during the active phase of the disease and should be tried only after suppression of vascular inflammation by appropriate IS treatment (84).

CSs are almost always the initial treatment, and conventional second-line IS agents such as methotrexate (MTX), azathioprine (AZA), mycophenolate mofetil (MMF), and leflunomide (LEF) are generally used alone or in combination to facilitate tapering the CS dose. Because of well-known potential adverse effects including gonadal toxicity, cyclophosphamide (CYP) is reserved for severe complications, as discussed in the following paragraphs. For patients resistant to these agents, i.e. for those with refractory disease, biologic agents including TNF inhibitors (TNFi), tocilizumab (TCZ), rituximab (RTX), and abatacept (ABA) may be added (27,85).

Before discussing the available evidence for each of these therapeutic agents, it should be stressed that, as with many other orphan diseases, the level of evidence for management of TAK is rather low. Except for a recently completed placebo-controlled randomized trial (86), most of the available data reflect the results of open studies, case series, and expert opinion. Therefore, currently it is not known whether a single conventional IS agent is more effective than others. Besides, there are no widely accepted criteria for definition of refractory disease activity to decide which patients warrant appropriate biologic treatment. In this regard, the Turkish Takayasu Arteritis Study Group issued a definition of refractory disease as shown in Table 2 (27,38,85).

## 10.1. Supportive measures

Although CS treatment is quite effective in TAK, metabolic side effects are important problems. Diet, low salt intake, calcium and vitamin D supplementation, and regular exercise are essential to reduce CS-related side effects. Monitoring and control of blood pressure may be difficult for patients with absent or reduced pulses in some extremities. Blood pressure measurements should be made in the unaffected extremities, including the lower extremities if necessary. In some patients with unreliable measurements, hypertensive retinopathy should be investigated as a warning sign for the clinician. The possibility of renovascular hypertension should be considered in the presence of treatment-resistant hypertension. In such cases, endovascular interventions or surgery may be necessary (27). Similar to other inflammatory diseases, the risk of atherosclerosis is also increased in patients with TAK (80). Therefore, preventive measures including use of antiplatelet agents should be considered. In the literature, there are a few studies favoring the use of antiplatelet agents in TAK (87–89). Furthermore, Numano et al. showed that antiplatelet therapy was associated with a lower frequency of ischemic events in patients with TAK (90). However, the relative efficacy of this treatment between different angiographic stages of TAK is not known (91).

## 10.2. Corticosteroids

In the presence of active disease, standard initial CS treatment is high-dose (1 mg/kg daily) prednisolone or its equivalents. Generally, two-thirds of the total daily dose is given early in the morning and the rest of the dose in the evening after meals. The response to high-dose CS is generally favorable, but relapses may occur while gradually tapering the dose. Besides, adverse effects of long-term treatment are devastating. Therefore, many physicians, including us, tend to start conventional IS agents together with the initial CS treatment or while tapering the CS dose (27,92,93).

## 10.3. Methotrexate

Since MTX is an inexpensive, easily available, and relatively safe agent that is widely used in rheumatology, it is the first choice of many physicians. However, data regarding MTX use in TAK are limited, consisting of case reports and a few small open studies (94–99). The most important data about the use of MTX in TAK come from the open study performed by Hoffman et al. in 1994 (98). They reported 16 patients with TAK given standard CS treatment plus MTX. Thirteen patients (81%) went into remission and eight patients (50%) remained in remission for a mean period of 18 months.

## 10.4. Azathioprine

AZA is another IS agent widely used for the treatment of TAK. Besides case reports (100,101), there is only one

**Table 2.** Definition of refractory disease in Takayasu arteritis as suggested by the Turkish Takayasu arteritis study group.

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Angiographic or clinical progression despite treatment or the presence of any of the following characteristics

Prednisolone dose >7.5 mg/day after 6 months of treatment, despite administration of conventional IS agents;

New surgery due to persistent disease activity;

Frequent attacks (more than three per year); and

Death associated with disease activity.

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open study from India (102). In this study, 65 IS agent-naïve patients with TAK were given 2 mg/kg AZA daily in addition to CS treatment for 1 year. At the end of the first year, acute phase responses were significantly reduced, no adverse events occurred, and control angiography showed no progression. However, long-term follow-up of these patients was not reported.

#### 10.5. Cyclophosphamide

CYP is a very potent and effective IS agent. In TAK, CYP is generally used in the presence of severe life- and/or vital organ-threatening conditions, including retinal vasculitis, pulmonary artery involvement with or without aneurysm, severe aortic regurgitation, or myocarditis, as reported in the literature (103–106). In a prospective study performed of TAK, seven patients resistant to CS treatment were additionally given 2 mg/kg oral CYP daily (106). After a mean period of 27.5 months, no clinical or radiological progression was observed in these patients. With respect to adverse events, hemorrhagic cystitis developed in two patients, herpes zoster in one, and oligomenorrhea in seven. In another open study, eight patients with TAK having myocardial involvement were reported to experience clinical hemodynamic and morphological improvement using CS plus CYP treatment (107).

#### 10.6. Mycophenolate mofetil

MMF is a promising agent in TAK. Three patients with TAK, resistant to CS plus MTX, were given MMF treatment (2 g/day) for at least 1 year with favorable clinical and radiological response (108). In the first open MMF study, 10 patients with treatment-resistant TAK were given MMF for a mean period of 23 months, resulting in significant reductions in acute phase proteins (109). Goel et al. reported the data of 21 consequent Indian TAK patients using MMF for  $9.6 \pm 6.4$  months (110). Among those patients, 10 had been resistant to CS plus AZA treatment. Using the ITAS and PGA, improvement in disease activity was shown. CS requirement was also reduced. The only adverse event reported was skin rash in a single patient. This study is notable for showing favorable efficacy and safety profile for MMF treatment in TAK.

#### 10.7. Cyclosporine and tacrolimus

Known as calcineurin inhibitors, CSA (111–113) and tacrolimus (114) were also tried in selected cases of

TAK with successful results. It has also been shown that CSA may be effective in the treatment of pyoderma gangrenosum complicating TAK (112,113,115).

#### 10.8. Leflunomide

LEF is a promising agent for TAK treatment. In addition to case reports of LEF use in TAK with promising results (116,117), the effectivity of LEF in treatment-resistant active disease was also shown in a prospective open-label study (118). In this study, 15 patients with TAK were given 20 mg of LEF daily. Disease activity was evaluated by Kerr's criteria and by the ITAS2010. Not only the short-term results of a mean follow-up of 9.1 months but also the long-term results of a mean follow-up of 43.0 months showed a favorable clinical response (119). Among 15 patients, follow-up information was available for 12 patients for the long-term report. While five (41.6%) TAK patients remained on LEF therapy, seven (58.3%) TAK patients had to switch to another therapy due to relapses in disease activity in six patients and toxicity in one patient.

#### 10.9. Tumor necrosis factor inhibitors

Given that vascular inflammation in TAK is granulomatous and vascular expression of TNF- $\alpha$  is abundant, TNFi agents are the first biologic agents tried for the treatment of TAK. Unlike GCA, TNFi agents were found to be effective in TAK, as reported in multiple retrospective observational studies (77,78,120). Analysis of 120 patients with refractory TAK receiving TNFi agents showed that infliximab (IFX) was the most commonly used agent (80%), while the remaining patients had used either etanercept (ETA) or adalimumab (ADA) (121). Overall response rate was 80%, and the CS dose could be reduced or discontinued in over 40% of the patients. However, relapses occurred in 37% of patients and nearly 50% of relapsing patients required either an increase in dose or frequency, or were switched to a different TNFi agent.

In another study the data of 49 patients with TAK who used various biological agents from different centers with a median treatment duration of 16 months (2–85 months) were retrospectively analyzed. Among those patients, 35 had received TNFi biologics (IFX 28, ETA 6, ADA 1). While 32 patients received TNFi agents as second-line treatment after resistance to conventional IS agents,



three patients had received these agents as the first-line treatment. Complete responses were seen in 35%, 61%, and 74% of the patients at months 3, 6, and 12, respectively. No relapse was observed in three years in 91% of the patients. However, during follow-up, at least one switch to another biologic agent was performed in 40% of the patients (122).

In summary, the results of observational studies as well as our personal experience confirm that TNFi agents may be beneficial in refractory TAK. Lack of randomized controlled trials with TNFi agents is an important problem preventing us from concluding the exact role of these agents in the treatment of TAK.

#### 10.10. Tocilizumab (TCZ)

Given that IL-6 has a critical role in the pathogenesis of TAK, TCZ, which is an IL-6 receptor inhibitor, is a promising agent for the treatment of TAK (123–125). The clinical efficacy of TCZ in TAK was first reported by Nishimoto et al. in 2008 (126). Following this initial case report, many studies reported beneficial effects of TCZ in patients with TAK having relapsing and refractory disease (127–133). The majority of the patients reported were treated with a TCZ dose of 8 mg/kg every 4 weeks, while a minority of patients were treated with 4 mg/kg every 4 weeks or 8 mg/kg every 3 weeks. In a retrospective analysis of 44 patients with TAK treated using TCZ, this agent was reported to be effective in the treatment of TAK in terms of clinical, biological, and radiological responses. TCZ was also reported to be a relatively safe steroid-sparing agent in TAK. TCZ may also be effective as rescue treatment for TAK patients resistant to TNFi agents (134).

Mekinian et al. (122) also reported 14 TAK patients who received TCZ, 11 of whom received it as second-line treatment after resistance to conventional IS agents. The other three patients had received TCZ as first-line treatment. Mekikian et al. reported that 29% of TAK patients treated with TCZ required at least one switch to another biologic treatment, suggesting that primary failure to TCZ may also be seen. Interestingly, the authors compared their patients treated with TCZ with those receiving TNFi agents and found that these two groups of patients were similar with respect to proportion of responders, vascular interventions, vascular complications, and relapse-free survival (122).

Overall, TCZ treatment was reported to be effective in TAK with more than 80% of patients having clinical and laboratory response within 3 months. Unfortunately, some of these patients experienced a relapse during treatment (85,125). As reported by Goel et al., although all of the 10 patients with TAK refractory to CS and second-line agents went into remission by the fourth infusion of TCZ, three patients (30%) relapsed both clinically and radiographically by the sixth infusion (127). More importantly, radiographic worsening occurred despite

normalized acute phase responses. This observation of silent vascular progression despite suppression of systemic inflammation with TCZ was also reported in other studies (48,132,133,135). Therefore, while evaluating clinical response, close monitoring with regular clinical assessment and serial imaging are obviously necessary during TCZ treatment (136). Even if some patients with TAK respond well to TCZ treatment, relapse is frequently seen at 2–6 months after discontinuation of TCZ (127). Even cytokine storm was defined after cessation of TCZ (137). It is unknown whether maintenance therapy with a conventional IS agent should be started when treatment with a biologic agent is discontinued.

Recently Nakaoka et al. reported the results of the first randomized, double-blind, placebo-controlled, phase 3 TCZ trial performed in Japan, the TAKT study (138). They included 36 patients with TAK who had relapsed within the previous 12 weeks and gone into remission with oral CS treatment. These patients were randomly assigned 1:1 to receive weekly TCZ at 162 mg or a placebo subcutaneously. Oral CSs were tapered 10% weekly from week 4 to a minimum of 0.1mg/kg daily until 19 patients relapsed. The primary endpoint was time to relapse of TAK, defined as  $\geq 2$  of the following: objective systemic symptoms, subjective systemic symptoms, elevated inflammation markers, vascular signs and symptoms, or ischemic symptoms. The per-protocol set (PPS) included 16 TCZ-treated and 17 placebo-treated patients. HRs for time to relapse of TAK were 0.41 (95.41% CI: 0.15–1.10;  $P = 0.0596$ ) in the intent-to-treat population (primary endpoint) based on relapse in eight TCZ-treated and 11 placebo-treated patients and 0.34 (95.41% CI: 0.11–1.00;  $P = 0.0345$ ) in the PPS. The secondary endpoints, time to relapse assessed by Kerr's definition and clinical symptoms only, were consistent with the primary endpoint. There were no serious infections and no deaths. Although the primary endpoint was not met in this trial, the authors concluded that TCZ was superior to the placebo for time to relapse of TAK without new safety concerns (138).

In summary, although TCZ appears to be effective and relatively safe in refractory TAK, information on its use in newly diagnosed patients naive to conventional IS agents or anti-TNF therapy is limited. Another phase III, open-label study evaluating the use of TCZ as first-line treatment in TAK is currently underway (ClinicalTrials.gov identifier: NCT02101333).

#### 10.11. Abatacept (ABA)

Assuming that inhibiting T-cell activation by means of blocking costimulatory signals may be helpful, abatacept was also tried in the treatment of TAK (139). However, case reports showing efficacy of ABA in patients with TAK are rare (139). A multicenter clinical trial that evaluated the efficacy of ABA concurrently for GCA and TAK was

also performed. Unfortunately, the results for TAK were disappointing. Treatment with ABA combined with prednisone did not provide a longer duration of relapse-free survival when compared to treatment with prednisone alone (86).

#### 10.12. Rituximab

Although TAK is accepted primarily as a T-cell-mediated disease, dysregulation of B-cell homeostasis was also suggested to contribute to its pathogenesis. Presence of both T and B cells was shown in the inflamed arterial adventitia of aortic wall samples from patients with TAK (140–142). Interestingly, while naive B cells are decreased, circulating newly generated plasmablasts and memory B cells are increased in patients with active TAK compared to inactive and control patients (142). Therefore, RTX, which is a chimeric anti-CD20 monoclonal antibody, was also tried in TAK (143,144). In the literature, there are case reports of RTX treatment in patients with refractory TAK who had not responded to conventional IS agents and/or TNFi biologics (142,145,146). RTX was generally used according to the protocol established for rheumatoid arthritis (1000 mg at days 0 and 15). RTX treatment was reported not only to result in clinical remission but also to reduce the expansion of newly generated plasmablasts in TAK cases (142). There are also case reports and suggestions for the use of RTX in TAK as a first-line IS agent (144,147). Recently, Pazzola et al. reported the results of seven TAK patients treated with RTX. While six patients had refractory disease, there was also a single newly diagnosed, treatment-naive TAK patient who had refused CS treatment and received RTX alone as a first-line IS agent. The authors concluded that RTX might have a role in some treatment-resistant TAK patients as second- or third-line biologic therapy, rather than as the first-line biologic therapy (51).

#### 10.13. Endovascular interventions and surgery

In the chronic stages of TAK, where there are persistent lesions that cannot be reversed by suppression of inflammation with medical treatment, endovascular interventions or surgery may be tried. If the problem is severe ischemia of any affected organ or extremity, such as hypertension caused by severe renal artery stenosis, cerebrovascular ischemia, coronary artery ischemia, or limb claudication, revascularization either by surgery or endovascular interventions including balloon angioplasty, stent, and stent graft replacement may be helpful (148–151). As a general rule, both endovascular interventions and surgery should not be performed during active disease. In other words, such procedures should be tried after suppressing systemic and vascular inflammation (148,149).

The success rate and outcome of endovascular interventions obviously depend on the site, length, and stage of the arterial stenosis. In the presence of short-

segment, critical arterial stenosis, balloon angioplasty or stent graft replacement may be useful. Percutaneous transluminal angioplasty is a less invasive and safe method; however, restenosis may occur in up to 77.3% of the procedures in the long term (152–154). If there is long-segment stenosis with extensive periarterial fibrosis or occlusion, surgical bypass of the affected segment is the procedure of choice and is clearly associated with superior results compared with endovascular interventions. The superiority of arterial surgical bypass reconstruction has been reported especially for lower limb and renal arteries (148–151,155).

Unfortunately, in-stent stenosis is an important complication. External stent compression by progressive vessel wall fibrosis and calcification was suggested to contribute to this complication (153,154,156). Although drug-eluting balloons and/or stents were offered to avoid or to minimize this complication, this topic is controversial. The use of drug-eluting systems may be useful to prevent intramural inflammation and severe intimal hyperplasia. Recently, Kazibudzki et al. reported a complicated case of TAK successfully treated with a drug-eluting balloon before stent implantation in the common carotid artery. According to these authors this strategy gave a higher probability of restenosis avoidance (154). However, there are also reports suggesting that such stents may increase the risk of early and late in-stent thrombosis (153,154,156).

On the other hand, antiplatelet treatment may not only lower the frequency of ischemic events in TAK (90) but also may decrease the likelihood of restenosis development, based upon the experience acquired from coronary interventions (157). Therefore, at least 6 months of dual antiplatelet therapy (27,157) as well as postinterventional IS treatment (158) are recommended to increase the success of endovascular interventions.

Other than bypass surgery for revascularization, other possible surgical indications for patients with TAK include progressive aneurysm enlargement having the tendency for dissection or rupture, moderate to severe aortic regurgitation, and severe aortic coarctation.

### 11. Prognosis of Takayasu arteritis

We believe that the duration and severity of both systemic and vascular inflammation, as well as major complications resulting from the vascular lesions, are important factors for prognosis. Late diagnosis and progressive disease course resistant to treatment may also cause poor prognosis. The presence of Takayasu retinopathy, renovascular hypertension, aortic regurgitation, aortic aneurysm, and/or comorbidities mostly resulting from CS treatment may also contribute to poor prognosis in TAK. In an old study performed in Japan for calculating 15-year survival rates in TAK, patients were stratified

based on three different parameters, namely presence or absence of a major complication, presence or absence of progressive disease course, and age at diagnosis (159). The reported 15-year survival rates were 66.3% vs. 96.4% for patients with and without a major complication, 67.9% vs. 92.9% for patients with and without a progressive course, and 58.3% vs. 92.7% for age >35 years vs. ≤35 years, respectively. Common causes of death in TAK include acute myocardial infarction, congestive heart failure, cerebrovascular accident, renal failure, and aneurysm rupture (15,160). In a recent study, reflecting the results of a large series with a long follow-up from the Mayo Clinic, USA, overall survival was much better compared to earlier series (97% at 10 and 86% at 15 years), although mortality was still increased compared to the general population (161). Similarly, Ohigashi et al. suggested that prognosis of TAK had improved over the last decade. Based on an analysis of 106 patients, they reported mortality of TAK as 2.8% during the 2000–2010 follow-up period (162).

Differences of mortality rates reported in different series may be explained by diverse disease phenotypes and severities due to ethnicity. Differences in medical therapy (e.g., less or more frequent use of CSs and cytotoxic agents) and variations in access to endovascular or surgical therapy may also affect the mortality rates (8).

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## 12. Conclusion

Although TAK is a challenging disease, increased awareness among physicians as well as the combination of careful physical examination, assessment of acute phase responses, and use of appropriate imaging studies may be helpful for early diagnosis. Discrepancies between systemic and vascular wall inflammation should always be kept in mind while assessing disease activity. There are current attempts to define better outcome measures for TAK. Combining new clinical features, acute phase responses, and the information from serial noninvasive imaging seems to be the most logical approach for assessing response to treatment and current disease activity. The rationale of medical treatment is to suppress inflammation with CSs and conventional IS agents. In cases of refractory disease activity, LEF, TNFi agents, and TCZ may be tried. In selected cases with persistent lesions that cannot be reversed with medical treatment, endovascular interventions including balloon angioplasty, stent and stent graft replacement, or surgery may be tried. However, such procedures should be performed after suppression of inflammation. The prognosis of TAK is probably getting better with lower mortality rates reported in recent years, probably due to the use of more effective medical treatments as well as the use of endovascular interventions when necessary and available.

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