Prognosis and Disease Activity

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Keywords

Prognosis · Disease assessment · Damage

Correct assessment of the extent of arterial involvement, clinical activity and damage in Takayasu's Arteritis (TAK) is essential for treatment or surgical intervention decisions during the disease course [1]. However, there are no widely accepted and validated definitions of "disease activity" or "response to treatment". One of the major difficulties is the differentiation between ongoing activity and vascular damage in TAK. Vascular stenosis may occur as a result of active inflammation or be a sign of disease-related damage due to scarring in the vessel wall [2]. Atherosclerosis is another important clinical problem in the assessment of TAK, especially in patients having long-standing disease or normal acute-phase response. There is a clear need and ongoing efforts to develop a validated set of outcome measures for use in clinical trials of TAK.

11.1 Disease Activity Assessment

11.1.1 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 for disease assessment in TAK. However, the limitations of physical examination for assessing disease

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extent was shown by Grayson et al. 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 [3]. In a recent study, a high specificity was detected between *newly developed* clinical symptoms and concurrent vascular imaging findings. Vascular imaging abnormalities are often present in a patient presenting with a specific head, neck and arm symptoms. However, presence of ischemic symptoms or even signs may not always indicate active inflammation of the vessel wall. In this context, carotidynia may be considered as a strong indicator of active inflammation, whereas limb claudication is usually a sign of vasculitis-associated damage in TAK [4].

11.1.2 Laboratory in Disease Activity Assessment

Erythrocyte sedimentation rate (ESR) and C-reactive protein are frequently advocated for disease assessment of TAK [5], despite being shown to be neither sensitive nor specific enough to monitor disease activity [6, 7]. In one study, active disease was present in the setting of normal laboratory parameters in 23% of the patients [8]. 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 [9]. Serum autoantibodies such as anti-aorta or anti-endothelial antibodies [10–12] and serum biomarkers such as TNF-α, IL-6, IL-8, IL-18, IFN-γ, MMP-2, MMP-9, YKL-40, APRIL and BAFF are shown to be elevated in TAK, but are not disease-specific [13–20]. Soluble IL-6R was recently suggested as a potential biomarker for disease activity in TAK patients [21]. In a recent study, it was suggested that increased serum FGF-2 level may distinguish TAK from giant cell arteritis, but needs to be confirmed [22].

Pentraxin (PTX) superfamily is a group of proteins recognizing a wide range of exogenous pathogens and behave as acute-phase response mediators [23]. PTX-3 was suggested to be a discriminative marker for active disease in TAK [24–26]. In a Turkish TAK cohort, patients had higher serum PTX-3 levels compared to healthy controls, but PTX-3 levels did not differ between active and inactive phases [27]. In an Italian TAK cohort, Tombetti et al. reported that only CRP was higher in active disease and PTX-3 levels were similar between active and inactive patients, similar to the Turkish study. However, significantly higher PTX-3 levels were observed in a subset of patients with 'detectable signs of vascular inflammation' shown with vascular imaging [28]. In a recent Chinese study, Serum PTX-3 level was found significantly higher in active TAK patients, but it was not superior to ESR or hsCRP for activity assessment in TAK [29]. Pulsatelli L. et al. recently assessed angiogenic markers in 33 TAK patients and reported that VEGF and PTX-3 significantly associated with disease activity determined by PET scan and activity indices (NIH, ITAS2010) [30]. The role of PTX-3 for activity assessment in TAK and its association with, especially, active lesions at imaging needs to be further investigated longitudinally.

11.1.3 Imaging in Disease Activity Assessment

Currently, conventional angiography is no longer considered as the 'gold standard' imaging tool for the diagnosis of TAK. Many physicians prefer to use MRA or CTA with FDG-PET-CT in selected cases for establishing the diagnosis of TAK. MRA is currently the 'gold standard' modality for the 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.

Exposure to large amounts of radiation and iodinated contrast limit the usefulness of CTA in routine follow-up. Recently, exciting preliminary reports have come up with PET-MRA with visual and quantitative results comparable to PET-CT. Improved soft-tissue resolution and definition of anatomy was reported with PET-MRA assessment using lower total radiation doses [31, 32]. However, further prospective research is needed with PET-MRA before it can replace other modalities for activity assessment. Imaging tools for the assessment of clinical activity in TAK were discussed in detail in the previous chapter.

11.1.4 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, APR or new angiographic features" is commonly applied in clinical studies [33]. Birmingham Vasculitis Activity Score (BVAS), documenting evidence of active vasculitis on a simple one-page form [34], is designed to apply to all vasculitides. However, BVAS is mostly used in therapeutic trials of ANCA-associated vasculitis and is validated for use only in small- and medium-vessel vasculitis. Most of the 11 organ systems in BVAS are not involved in TAK [35] and only two studies have used BVAS [36, 37]. The "disease extent index for Takayasu's arteritis (DEI.TAK)" was developed as an assessment/disease extent tool in which items corresponding to large arterial disease carry greater weights than general items of the disease and changes in the prior 3 months in the physical examination are the basis of evaluation [38]. In a study from Turkey, most patients with slow progression of disease demonstrated no change in the DEI.TAK score. As DEI.TAK was substantially derived from BVAS, most items are related to small-vessel vasculitis and were not involved or did not change in patients with TAK. Furthermore, discriminant ability of the instrument was not high. Among the DEI.TAK (−) group, 31% were felt to have "active/persistent" disease according to the physician's global assessment (PGA) while 18% of patients with a DEI.TAK score ≥1 were considered inactive by PGA. PGA and DEI.TAK had only modest agreement (68%) [35].

In 2010, a new version of DEI.TAK, the Indian Takayasu's Arteritis Score (ITAS) was introduced [39]. ITAS2010 has only six systems and scoring is weighted for vascular items (0–2). ITAS2010 seems to have a sufficient comprehensiveness and

the inter-rater agreement is better than (PGA) (0.97 vs 0.82). However, convergent validity, when assessed by comparison to PGA, is quite low at the initial evaluation but improved at subsequent study visits (r = 0.51, 0.64, and 0.72). Although CRP and ESR had weak correlations with ITAS2010, the authors also incorporated acute-phase response to the score (ITAS2010-A) by adding an extra 1–3 points for elevated ESR or CRP. This change resulted in higher ITAS2010-A scores both in active and inactive patients, and a cut-off of 4 points is suggested for a definition of active disease [40]. In a study of Turkish patients during routine follow-up, ITAS2010 was significantly higher in patients with active disease. However, total agreement between ITAS2010 and PGA was again moderate (66.4%), but was better between ITAS2010 and NIH score (82.8%). During follow-up, 14 of 15 patients showing vascular progression with imaging were categorized as having inactive disease according to ITAS2010. Low correlation of ITAS2010 with PGA suggests that physicians seem to accept some patients only with increased APR or new abnormalities on vascular imaging studies (such as new vessel wall enhancement or thickening observed by MRI or PET) as "active," which were below the cut-off values of ITAS2010 for active disease [41]. In a recent study, ITAS2010 was combined with imaging. A total of 410 visits in 52 patients were evaluated with 3–6 monthly B-mode/Doppler ultrasonography (US) and 6–12 monthly MRI/MRA. An additional point was added to ITAS2010-A if there is radiologically active disease which was defined as the presence of new major involvement and mural contrast enhancement/edema on MRI/MRA, or arterial wall thickness on US compared to the previous assessment. This new scoring was labeled as ITAS-A-Rad. The agreement was found to be 76% between Rad-Active and PGA, 83% between Rad-Active and Kerr et al.'s criteria. Both the agreements of ITAS2010 and acute-phase reactants with PGA (69% and 60, respectively) and also Kerr et al.'s criteria (78% and 42%, respectively) were lower compared to those of Rad-Active. Mean ITAS-A-Rad scores were higher in visits with active disease according to PGA and Kerr et al.'s criteria [42]. This study showed that imaging should be a part of activity assessment in TAK. Further prospective validation studies are needed to confirm these results.

The 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. However, as all items are not required to be included in an activity index, a data-driven approach for item reduction is needed [43].

Recently, EULAR suggested new definitions for active disease, relapse, and remission (Tables 11.1 and 11.2). But these new definitions are consensus-based and do not derive from a systematic literature review. EULAR suggest using the term "relapse" and avoiding the term "flare." These definitions seem acceptable, but needs to be tested in prospective studies [44].

Table 11.1 EULAR consensus definitions for disease activity states in large-vessel vasculitis

Activity state	EULAR consensus definition
	1. The presence of typical signs or symptoms of active LVV (Table 11.2) 2. At least one of the following: (a) Current activity on imaging or biopsy (b) Ischemic complications attributed to LVV (c) Persistently elevated inflammatory markers (after other causes have been excluded)
Flare	We do not recommend use of this term
Relapse	We recommend use of the terms major relapse or minor relapse as defined below
Major relapse	Recurrence of active disease with either of the following: (a) Clinical features of ischemia (including jaw claudication, visual symptoms, visual loss attributable to GCA, scalp necrosis, stroke, limb claudication) (b) Evidence of active aortic inflammation resulting in progressive aortic or large-vessel dilatation, stenosis, or dissection
Minor relapse	Recurrence of active disease, not fulfilling the criteria for a major relapse
Refractory	Inability to induce remission (with evidence of reactivation of disease, as defined above in "Active disease") despite the use of standard care therapy
Remission	Absence of all clinical signs and symptoms attributable to active LVV and normalization of ESR and CRP; in addition, for patients with extracranial disease there should be no evidence of progressive vessel narrowing or dilatation (frequency of repeat imaging to be decided on an individual basis)
Sustained remission	1. Remission for at least 6 months 2. Achievement of the individual target GC dose
Glucocorticoid-free remission	Sustained remission Discontinued GC therapy (but could still be receiving other immunosuppressive therapy)

Table 11.2 Key symptoms and clinical findings suggestive of active large-vessel vasculitis

Takayasu arteritis
Key symptoms
• New onset or worsening of limb claudication
• Constitutional symptoms (e.g., weight loss >2 kg, low-grade fever, fatigue, night sweats)
• Myalgia, arthralgia, arthritis • Severe abdominal pain
• Stroke, seizures (non-hypertensive), syncope, dizziness
• Paresis of extremities
• Myocardial infarct, angina
• Acute visual symptoms such as amaurosis fugax or diplopia
Key findings on clinical examination
• Hypertension (>140/90 mmHg)
• New loss of pulses, pulse inequality
• Bruits
• Carotidynia

11.2 Prognosis

11.2.1 Disease Course

TAK generally has a relapsing-remitting course leading to prolonged periods of seemingly clinically "inactive" disease during which arterial damage can still progress. Due to lack of standardized assessment tools, physicians generally manage the cases with TAK according to PGA as the "gold standard" in daily practice, combining subjective clinical symptoms, laboratory markers and imaging. Relapses are frequent in TAK during the disease course [45]. A significant subset of TAK patients (44%) developed new severe manifestations during their follow-up in the VCRC cohort from the USA [46]. In a series of Korean patients in remission, 22% had a relapse during a follow-up of 37 months, which is mainly associated with Type V disease, suggesting that low-level inflammation is associated with the extent of the disease [47]. Interestingly, disease starting >40 years is observed to have fewer relapses with lower initial doses of corticosteroids for remission induction in Japan [48]. In a retrospective French cohort including 318 patients, during a median follow-up of 6.1 years, relapses were observed in 43%, vascular complications in 38%, retinopathy in 4%, and death in 5%. The 5- and 10-year relapse-free survivals were 36.4% (30.3; 43.9) and 69.9% (64.3; 76.0), respectively. Multivariate analysis showed that relapses were more common in patients with elevated CRP levels, carotidynia, and male gender. This study also showed that almost half of patients with TAK will relapse and experience a vascular complication ≤10 years from diagnosis [49]. In a recent, retrospective Korean study, it was reported that statins may be beneficial in reducing relapse rate after achieving remission [50].

As in other inflammatory disorders, accelerated atherosclerosis is a possible risk factor for increased morbidity and mortality in TAK. There are very few data about the risk of cardiovascular (CV) disease and atherosclerotic burden in TAK. Seyahi et al. first showed that the frequency of atherosclerotic plaques is increased in TAK, similar to SLE a disease associated with systemic premature atherosclerosis [51]. Da Silva et al. also found a high prevalence of metabolic syndrome in patients with TAK [52]. There are also a few studies favoring the use of antiplatelet agents in TAK [53–55]. Recently, in a comparative study of patients from the USA and Turkey, CV risk factors were more common in patients with TAK, particularly hypertension. The Framingham 10-year general CV risk score at the time of diagnosis and the cumulative incidence of CV events were higher during follow-up in patients with TAK. However, aspirin usage had no significant effect on the risk of CV event development [56]. In another study from Brasil, aspirin usage with doses of 100–200 mg/day reduced the risk of ischemic events in TAK [57]. According to 2018 Update of the EULAR recommendations for the management of large-vessel vasculitis, aspirin should not be routinely used for the treatment of LVV unless it is indicated for other reasons (e.g., coronary heart disease, cerebrovascular disease) [37]. Overall, current data suggest that patients with TAK should undergo careful assessment of CV risk factors, and an aggressive risk modification approach is warranted.

11.2.2 Damage Assessment in TAK

Treatment of TAK is usually focused on the prevention of disease-related damage [58]. But, it is critical to differentiate irreversible damage from disease activity and thus avoid potential over-treatment with toxic agents such as corticosteroids. Angiographic findings may not demonstrate whether changes in the vessel wall are associated with active vascular inflammation or irreversible damage [59]. Vasculitis Damage Index (VDI) has been the standard tool for assessing damage in small-vessel vasculitis. In the development and validation study of VDI which had only six TAK patients out of 100, 95% had at least one damage item at baseline [60]. In a large series from Turkey, VDI was assessed in 165 TAK patients with a mean follow-up of 60 months. VDI scores in TAK were moderately high (mean: 4 (1–12)) and were mainly due to the disease itself with major vessel occlusion. Still, 39% also had treatment-related damage with osteoporosis/vertebral fractures the main causes. Age, resistant disease course, disease duration, and cumulative corticosteroid doses were independently associated with damage, suggesting that, even in experienced centers, accumulation of damage is a major challenge in the management of TAK patients [61].

Another damage score, Takayasu Arteritis Damage Score (TADS), derived from DEI.TAK, was developed to evaluate the cumulative damage in only TAK patients. The scoring system consists of seven categories, which are mainly focused on the cardiovascular system [35, 62]. In a recent study comparing VDI and TADS, median VDI score was 4 (1–8) and median TADS score was 7 (1–15) at baseline assessment. At the end of the follow-up (app. 77 months), the median VDI score was 5.0 (1–17) and median TADS score was 8.0 (1–19). The median number of disease-related items were higher in TADS scoring (8 items vs 4 items). At least 1 new corticosteroid-related damage item occurred in 35 patients (31%). Older age at symptom-onset and cumulative CS doses were predictor factors for higher VDI score (≥5). Also, age at symptom-onset and disease duration were associated with an increase in TADS (≥8). Gender and number of relapses were not found to be associated with damage scores. The results confirmed that damage assessment with VDI seems to be predominantly evaluating the treatment-related damage, whereas TADS provides more detailed information on disease-related damage in TAK (*Kaymaz-Tahra S, unpublished*). Therefore, both disease-related and treatment-related damage must be considered while monitoring the disease. Another assessment tool for damage, large-vessel vasculitis index of damage (LVVID) score, are in the development phases by VCRC. LVVID includes additional items in the ocular, cardiac, and peripheral arterial categories which are mainly involved in large-vessel vasculitis and are missing on the VDI [63].

11.2.3 Mortality

Although data is showing better prognosis in recent studies, there is still a significant delay in the diagnosis of TAK. Both morbidity and mortality rate is still high

due to new and severe manifestations after diagnosis [64]. In an old study, Ishikawa et al. developed a prognostic scoring system with three stages based on three different parameters, namely the presence or absence of major complications (defined as at least one of the following: microaneurysm formation, severe hypertension, grade 3 or 4 aortic regurgitation), presence or absence of progressive disease course, and age at diagnosis. Survival rate at 15 years was 43% in stage 3 (major complication, progressive course with/without high ESR). But, in stage 1 (patients without major complications nor progressive course with high ESR or patients with only low ESR, or patients with progressive disease, high ESR but without major complications), 15 years survival rate was 100%. Major causes of death were congestive heart failure, acute myocardial infarction, cerebrovascular accidents, and postoperative complications [65]. Soto et al. reported a decrease in overall survival rates over time, 92%, 81%, and 73%, respectively, at 2, 5, and 10 years after diagnosis in Mexican TAK patients. Systemic arterial hypertension, coronary heart disease, and aortic valve regurgitation were found as predictors for mortality [66]. In 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), but mortality was still increased compared to the general population [67]. In a recent French TAK cohort including 299 patients, 47 (16%) TAK patients presented at least one ischemic or aneurysmal complication or died during follow-up. The 5- and 10-years event-free survival was 81% (95% CI: 76–87) and 75% (95% CI: 68–82) in TAK [68]. Secondary hypertension, congestive heart failure, and longer disease duration were main factors for mortality in another series of Chinese patients [69]. In recent French Vasculitis Network series assessing 318 patients, mortality was 5% in a median follow-up of 6.1 years. In multivariate analysis, progressive disease course at diagnosis, thoracic aorta involvement, and retinopathy were independently associated with death and complication-free survival. The authors suggested a prognostic score based on this model as low and high risk for the probability of death and complication-free survival according to the presence of progressive disease course, thoracic aorta involvement, and retinopathy. If there is none of the three selected factors or presence of one factor at diagnosis, score is categorized as low risk. If there is 2 or 3 factors, the score is categorized as high risk. The probability of death and complication-free survival at 1 year in the low risk vs. high risk groups was 90.7% vs. 78.6% and at 5 years 78.4% vs. 51.5% [70]. 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 [71].

11.3 Conclusion

Biomarkers (ESR, CRP) have limited value for activity assessment in TAK. PTX-3 was recently suggested as a discriminative test for clinical activity, but the results are controversial and needs to be further investigated—especially longitudinally.

Currently, conventional angiography is no longer considered as the "gold standard" imaging tool for the diagnosis of TAK. Many physicians prefer to use MRA or CTA with FDG-PET-CT in selected cases for establishing the diagnosis of TAK. MRA is the gold standard modality for the longitudinal follow-up patients with TAK. Compared to DSA, three-dimensional MRA can effectively show vessel wall thickening, whereas contrast-enhanced MRA allows better soft-tissue differentiation for the assessment of disease activity. Exposure to large amounts of radiation and iodinated contrast limit the usefulness of CTA in routine follow-up. Recently, exciting preliminary reports have come up with PET-MRA with comparable visual and quantitative results to PET-CT. Improved soft-tissue resolution and definition of anatomy was reported with PET-MRA assessment using lower total radiation doses. New tools for disease assessment such as ITAS2010 aim to better characterize and quantify disease activity.

Prognosis is recently possibly getting better with lower mortality, but a substantial damage is present even in early cases. There is a clear need to develop a validated set of outcome measures to be used in clinical trials of TAK. The OMERACT Vasculitis Working Group has taken on this task, finished a Delphi exercise with experts and aims to develop a core set of outcomes for LVV.

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