REVIEW ARTICLE

Takayasu's Arteritis- A Review

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Summary:

Takayasu's arteritis (TA) is a rare, idiopathic, chronic inflammatory disease with cell-mediated inflammation, involving mainly the aorta and its major branches. It leads to stenosis, occlusion or aneurysmal degeneration of large arteries. The clinical presentation is characterized by an acute phase with constitutional symptoms, followed, months or years later, by a chronic phase in which symptoms relate to fibrosis or occlusion of vessels. Conventional angiography, the gold standard method for initial diagnosis, appears to have been replaced with new imaging modalities such as magnetic resonance angiography (MRA) and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) in recent years. These are also used for the assessment of disease activity. New tools for disease assessment such as Indian Takayasu's Arteritis Score 2010 (ITAS2010) and color Doppler ultrasound (CDUS) aim to better characterize and quantify disease activity. Leflunomide, tumor necrosis factor (TNF)-± antagonists, and tocilizumab are new options for patients resistant to conventional therapies. Prognosis is possibly getting better, with lower mortality in recent years due to recent advancement in investigations and management.

Key words: vasculitis, Takayasu's arteritis, pulseless disease, disease assessment, outcome.

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Introduction

Takayasu's arteritis (TA) is a rare, chronic large-vessel arteritis that predominantly affects the aorta, its major branches, and the pulmonary arteries. Segmental stenosis, occlusion, dilatation, or aneurysm formation may occur in the vessel wall during the course of the disease.[1-4] All large arteries can be affected, although the ascending/descending aorta, subclavian arteries, and extra cranial arteries such as carotids are most frequently involved (60%–90%). The disease generally has a prolonged indolent course. Clinical feature varies from constitutional features (fever, malaise, anorexia, and weight loss) to visual loss or stroke. Absent or diminished pulses, bruits, and absent blood pressure can be present according to the vessel involved.[5]

Given the rarity of TA, the search strategy needed to be comprehensive, allowing varied study designs (RCTs, and observational prospective and retrospective studies). By including high-quality evidence from RCTs, and potentially lower quality evidence from small observational studies such as cohorts or case series, we aimed to ensure that the results better reflect clinical practice. To maximise results, a wide and indepth search was conducted encompassing the Medline, Embase and Cochrane libraries.

In this review, we will summarize the recent developments in the diagnosis, clinical course, disease assessment with biomarkers/imaging, outcomes, and new treatment options of TA.

Epidemiology

TA has world-wide distribution, but prevalent in Asian populations.[6,7] It was first reported in 1908 by Japanese ophthalmologists.[8,9] TA is seen predominantly in young women (female: male ration 8:1) with a typical onset at the age of 25-30 years.[10-11] A comparative study from France investigated TA among white, North African, and black patients.[12] The median age at diagnosis was 39.3 years in white, 28.4 years in North African, and 28.0

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years in black patients. Some hospital based studies reflect the incidence of 1-2 cases per million,[13] According to a nationwide Japanese registry, there were at least 5881 patients with TA in Japan in 2011, with the prevalence believed to be over 0.004%.[14]

Aetiopathogenesis and histology

The aetiopathogenesis of the disease has not been clarified yet. Infections, autoimmunity and genetic factors have been proposed as aetiologic factors. Viral infection is being investigated as a trigger of vasculitis, because vascular lesions are similar to those found in animals with viral infections.[15] Concerning the autoimmune hypothesis, Seko[16] has reported that ³′T cells, ±²T cells and natural killer cells play an important role in vascular injury. Moreover, in affected patients anti-endothelial cell antibodies also have been reported.[17-19] TA has been described in monozygotic twins, suggesting the involvement of genetic factors in the aetiopathogenesis of the disease.[20] Different human leucocyte antigen (HLA) alleles have been associated with the disease in different ethnic groups and correlated with different clinical phenotypes[21]: in Japan there is a clear association with the HLA-B52 and B39 alleles.[22] Histological features in the acute phase of TA is characterized by a panarteritis extending from the adventitia to the media in which T-lymphocyte and dendritic cell infiltrates present in the adventitia and media is infiltrated by lymphocytes and occasional giant cells with neovascularisation.[23,24] In the chronic phase, this process leads to a thickening of the whole vessel wall: the adventitia is fibrotic, the media is fragmented because of the destruction of elastic fibres and the proliferation of the intima causes a reduction of the vessel lumen. The development of arterial aneurysms, less frequent than stenosis, is probably due to the lack of fibrotic tissue or to a localized weakness of the intima.

Clinical manifestations

TA course can be divided into three consecutive phases: an early phase characterized by constitutional features such as fever, weight loss, malaise, headache and nocturnal sweats; a vascular phase characterized by symptoms due to stenosis, occlusion or aneurysms; a final phase in which the disease is "burntout" or in clinical remission.[25] However, all these three phases rarely occurs in affected patients . Table 1 shows the most common symptoms of TA in the overall course of the disease in a large cohort of patients.

Table-I

Clinical manifestations of Takayasu's arteritis.

Symptoms	%
Vascular	100
Carotid bruit	70
Claudication of	
Upper limbs	62
Lower limbs	32
Pulse deficit on	
Upper limbs	53
Lower limbs	15
Carotodynia	32
Femoral bruit	3
Renal bruit	2
Neurological	57
Dizziness	33
Visual aberrations	20-30
Visual loss	< 10
Stroke	< 10
Transient ischaemic attack	< 10
Muscoloskeletal53	
Chest wall pain 30	
Joint pain 30	
Myalgia 10-20	
Constitutional	43
Malaise	30-40
Fever	20-30
Weight loss	20
Night sweats	< 5
Cardiac	38
Aortic regurgitation	20
Angina	10
Palpitations	< 10
Congestive heart failure	< 10
Pericarditis	< 5
Myocardial infarction	< 5

Classification of TA

The first clinical classification was proposed by Ishikawa[26] in 1978: it implies four levels of severity and it is based on the natural history of the disease in absence of specific treatment and on vasculitis complications (Table 2). Some studies supported this classification as regards prognostic assessment.[27,28] In one Indian study, cumulative survival at 5 years after disease onset was 91% and 84% at 10 years.

Nevertheless, these criteria are difficult to apply in every country because they are primarily based on Japanese patients.

In 1990, the American College of Rheumatology proposed a simple classification to diagnose TA, differentiating it from other vasculitis[29] (Table 3). This classification is simple and easy to use, but it does not recognize other clinical features that may be taken into consideration for purposes of clinical diagnosis such as fever, arthralgias, weight loss, hypertension, elevated erythrocyte sedimentation rate (ESR) and anaemia. Therefore in 1995 Sharma et al[30,31] modified Ishikawa's criteria, abolishing the obligatory criterion of age and including the presence of at least 1 month of characteristic signs and symptoms (Table 4).

Investigations

Laboratory search for a biomarker

As in other inflammatory disorders, search for a convenient, reliable, and validated biomarker for TA still continues. Acute phase reactant evaluation ESR and CRP levels are frequently advocated for disease assessment in TA, despite being shown to be neither sensitive nor specific enough to monitor disease activity.[3] ESR was elevated in only 72% of patients considered to have an active disease and was still high in 44% of patients considered to be clinically inactive. Serum autoantibodies such as anti-endothelial antibodies[32], serum biomarkers such as IL-6, IL-8, IL-18, and matrix metalloproteinase-9[33,34] have been suggested as biomarkers of TA.

Recently, pentraxin 3 (PTX3), which is produced by immune and vascular cells in response to proinflammatory signals, was suggested as a biomarker for disease activity. In a study from Japan, among the 28 patients with active TA, 71% were positive for CRP and 82% for PTX3. [35-37]

Imaging in TA: recent developments

The earliest detectable abnormality is usually the thickening of the vessel wall by inflammation in TA. Magnetic resonance angiography (MRA), ultrasound (USG), and to a lesser degree, computed tomography (CT) can detect vessel wall thickening. Conventional

Table-II

Ishikawa clinical classification of Takayasu arteritis.

Group	Clinical features
Group I	Uncomplicated disease, with or without pulmonary arteryinvolvement
Group IIA	Mild/moderate single complication together with uncomplicateddisease
Group IIB	Severe single complication together with uncomplicated disease
Group III	Two or more complications together with uncomplicated disease

Table-III

American College of Rheumatology criteria for clinical diagnosis of Takayasu's arteritis.

Criterion	Definition
1.Age at disease onset < 40 years	Development of symptoms or findings related to Takayasu arteritis at age < 40 years
2.Claudication of extremities	Development and worsening of fatigue and discomfort in muscles of one or more extremity while in use, especially the upper extremities
3.Decreased brachial artery pulse	Decreased pulsation of 1 or both brachial arteries
4.Blood pressure difference > 10 mmHg	Difference of > 10 mmHg in systolic blood pressure between arms
5.Bruit over subclavian arteries or aorta	Bruit audible on auscultation over one or both subclavian arteries or abdominal aorta
6.Arteriogram abnormality	Arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper and lower extremities, not caused by atherosclerosis, fibromuscular dysplasia, or similar causes; changes usually focal or segmental

A diagnosis of Takayasu's arteritis requires that at least three of the six criteria are met.

Table-IV

Sharma modified criteria for clinical diagnosis of Takayasu's arteritis.

Major criteria	
1.	Left midsubclavian artery lesion: stenosis or occlusion 1 cm proximal to the left vertebral artery orifice up to 3 cm distal
2.	Right midsubclavian artery lesion: stenosis or occlusion from the right vertebral artery orifice to 3 cm beyond
3.	Characteristic signs and symptoms (> 1-month duration)
	A. Limb claudication
	B. Pulselessness or blood pressure differential > 10 mmHg in arms
	C. Exercise ischaemia
	D. Neck pain
	E. Fever
	F. Amaurosisfugax
	G. Syncope
	H. Dyspnoea
	I. Palpitations
	J. Blurred vision
	Minor criteria
	1.High ESR : Westergren ESR > 20 mm/h
2.	Carotodynia
3.	Hypertension: brachial blood pressure > 140/90 mmHg o popliteal blood pressure > 160/90 mmHg
4.	Aortic regurgitation or annuloaorticectasia: determined by auscultation, arteriography or echocardiography
5.	Pulmonary artery lesion: lobar or segmental artery occlusion, or stenosis or aneurysm of pulmonary trunk
6.	Left middle common carotid artery lesion: stenosis or occlusion of middle 5 cm portion starting 2 cm from its orifice
7.	Distal innominate artery lesion: stenosis or occlusion in the distal third
8.	Descending thoracic aorta lesion: narrowing, aneurysm, or luminal irregularity
9.	Abdominal aortic lesion: narrowing, aneurysm, or luminal irregularity
10.	Coronary artery lesion: documented by arteriography in patients < 30 years of age and without risk factors foratherosclerosis

Two major, or one major and two minor, or four minor criteria indicate a high probability of Takayasu's arteritis. ESR, erythrocyte sedimentation rate.

digital subtraction angiography is the "gold standard" for detecting stenosis, occlusions, and aneurysms that characterize the latter stages of TA; however, it is the least sensitive method for visualizing wall thickness.

Angiogram

Angiography allows a topographic classification which correlates anatomic involvement, clinical manifestations and prognosis: in 1994 the Takayasu Conference in Tokyo proposed an angiographic classification of TA that allows to distinguish different subgroups of patients (Figure-1 and Table 5).[38]

Computed tomography(CT) / Magnetic resonance Angiography(MRA)

Contrast-enhanced MRA or CT angiography (CTA) allows non-invasive imaging of the aorta and its major

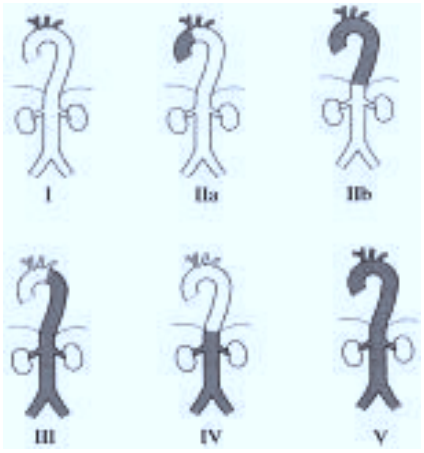


Fig.-1. *Angiographic classification of Takayasu's arteritis.*

Table-V

Angiographic classification of Takayasu's arteritis.

Type	Vessel involvement
Type I	Branches from the aortic arch
Type IIa	Ascending aorta,aortic arch and its branches
Type IIb	Ascending aorta,aortic arch and its branches,thoracic descending aorta
Type III	Thoracic descending aorta,abdominal aorta and/or renal arteries
Type IV	Abdominal aorta and/or renal arteries
Type V	Combined features of types IIb and IV

According to this classification system, involvement of the coronary or pulmonary arteries should be designed as C(+) or P(+),respectively.

branches. Recently, MRA has become popular for the diagnosis of TA (Figure-2). Compared with invasive angiography, three-dimensional MRA can effectively show vessel wall thickening. Contrast-enhanced MRA allows better soft-tissue differentiation and can depict other signs of inflammation, including mural edema and increased mural vascularity. Advantage of MRA is the lack of iodinated contrast material and also has the potential to assess disease activity and response to treatment.[39-41]

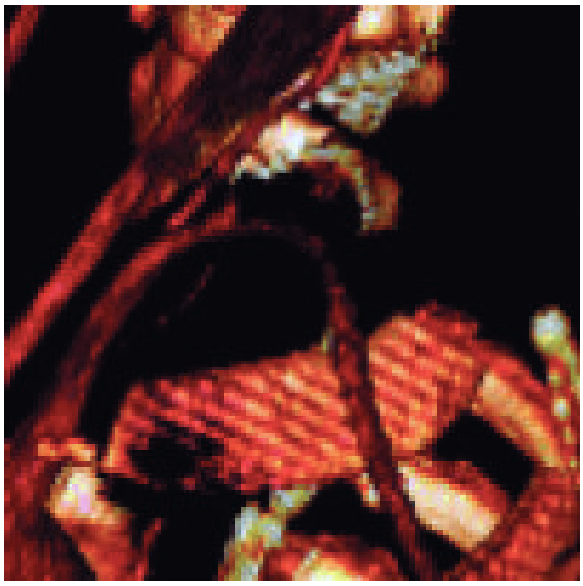


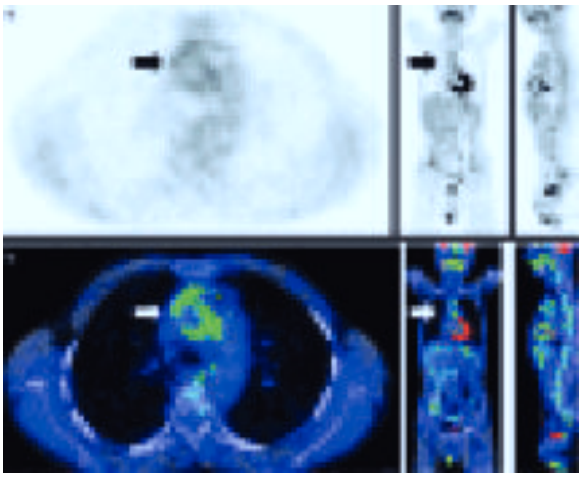
Fig.-2: *Three-dimensional reconstruction of computed tomography angiography (CTA) data demonstrating high-grade stenosis in the left subclavian artery.*

Ultrasonography (USG)

As a non-invasive modality, USG has recently been extensively studied in TA, particularly to investigate the changes in carotid arteries. Doppler USG can detect stenosis in carotid arteries with high sensitivity (90%) and specificity (91%).[42] Contrast-enhanced USG may allow the identification of vessel wall thickness, inflammation-driven hyperemia and neovascularization, a potential marker of disease.[43,44] A scoring system for TA assessment with color Doppler USG (CDUS) has also been recently presented.[45] However, intrathoracic vessels, such as the commonly involved subclavian arteries, were particularly difficult to visualize.

18F-fluorodeoxyglucose positron emission tomography (FDG-PET)

FDG-PET, is an operator-independent, non-invasive metabolic imaging method based on the regional distribution of the glucose analogue 18F-FDG, (Figure-3). Some studies quantify 18F-FDG uptake using a standard uptake value (SUV), whereas others use a semi-quantitative method comparing the 18F-FDG uptake of a vascular region of interest (ROI) with that of the liver using a 0–3 grading system [0=no uptake present; 3=high-grade uptake (uptake higher than that by the liver uptake)].[46-48]In a study on 38 patients, 18F-FDG uptake was associated with clinical disease activity and markers of inflammation, and FDG-PET reflected changes in clinical disease activity.[49] In a meta-analysis of the literature, the pooled sensitivity and specificity of 18-FDG-PET were found to be 70.1% and 77.2%, respectively.[50]



X-ray

Chest X-ray may be used for diagnosis of TA. Linear calcifications of the arch of aorta and the thoracic descending aorta without the involvement of the ascending aorta may suggest a TA in the late phase.

Differential diagnoses

Certain congenital condition affecting tissue matrix may mimic TA. Marfan and Ehler-Danlos syndromes affect aorta and may mislead the correct diagnosis, however these condition are not associated with stenotic lesion of large vessels that is a common feature of TA.[51,54] Some autoimmune conditions such as systemic lupus erythematosus (SLE), temporal arteritis, Cogan syndrome and Behçet's disease are associated with large vessel vasculitis and may present with the features like those of TA.[55] However, these conditions have their own specific features differentiating them from TA. Sarcoidosis is also associated with stenotic heart leasions but it can be excluded with the evidence of its characteristic features of skin lesions, hilar adenopathy and Bell's palsy.[51-56]

Treatment

Medical treatment

Steroid is the mainstay of treatment for TA and reports of efficacy vary. This may relate to the stage of disease at which treatment is introduced in addition to disease extent. Early data suggested little benefit,[57] with six of eight patients treated showing no improvement. In a study, of 48 treated patients, remission was achieved at least once with steroids alone in 60%.[58] It is now accepted that approximately half of patients treated with steroids will respond.[59] This lack of universal success and the side effects associated with steroid use have led to a search for a more effective treatment.

Immunosuppressive agents including cyclophosphamide, azathioprine, and methotrexate (MTX) have all been tried in different studies. In a study on 25 steroid unresponsive patients receiving cytotoxic medications including cyclophosphamide, azathioprine, or MTX, although not concurrently. The overall remission rate was 33%. 23% of all treated patients in their study never achieved remission. [58] No single cytotoxic drug appears to be better than any other in terms of efficacy. Side effect profiles have been an important factor in determining treatment. A study of 16 steroid unresponsive patients treated with MTX and steroid demonstrated remission in 81%.[60] More recently, three patients have been reported after treatment with mycophenolate mofetil. All three showed clinical benefit, steroids were tapered or discontinued, and no toxicity was observed. [61]

Recent uncontrolled data of leflunomide, tumor necrosis factor (TNF)-± antagonists, and tocilizumab (TCZ) in refractory TA appear promising.[62] Leflunomide was shown to be effective in a short-term study of 14 patients with active TA despite therapy with corticosteroids and other immunosuppressive agents. In this study, disease activity decreased with leflunomide (from 93% to 20%) and mean daily dose of prednisone also decreased from 34.2mg-13.9 mg. Evidence for the use of TNF inhibitor (TNFi) in TA was described in open-label studies only. In a prospective trial, Hoffman *et al* [85] suggested benefit from TNFi [etanercept (ETA) or infliximab (IFX)] in refractory TA. However, the use of TNFi was associated with progression of imaging changes (in 4 out of 15 patients) despite apparent complete clinical or partial remission defined as absence of features of active disease, or new lesions on sequential imaging and no glucocorticoid (GC) therapy or with GC dose reduced by ≥50%. Among biological agents, TCZ is currently the most popular and has been studied in 9 case series and some individual cases in the last 5 years.[63-70] A recent literature review summarized 44 cases in 2013, with a mean follow-up period of 9 months.[71] As sustained remission could only be achieved with long-term treatment in most patients, different biological agents may be required during long-term follow-up. A retrospective multicentre analysis of patients with TA

(n=49) treated with TNFi or TCZ found no significant differences in safety and efficacy, even though there was one case of tuberculosis (TB) reactivation in a patient treated with TNFi (IFX).[86]

A descriptive prospective cohort study assessing the effects of escalating therapy with conventional synthetic DMARDs and then with biologic DMARDs (TNFi or TCZ) in refractory TA not responding to GC demonstrated that 64% of patients achieved and maintained remission with bDMARD treatment.[87] There was one retrospective case series (n=7) of refractory TA treated with rituximab as first-line bDMARD, but despite treatment four out of seven patients still had persistent disease at follow-up.[88]

The other important medical issues relate to the management of hypertension and the prevention and treatment of thrombosis. Hypertension can be particularly difficult, and worsened by the use of steroids with their fluid retaining side effects. Management of hypertension in patients with TAK due to multifactorial causes (renal arteries or aortic stenosis) was retrospectively described in a cohort of 381 patients,[74] with many patients requiring intensive medical treatment with e"3 different antihypertensive drugs combined with immunosuppressive agents (GC and/or csDMARDs) and revascularisation procedures. For the treatment of thrombosis, thrombolytic agents like streptokinase and/or low molecular heparin/ conventional heparin, other anticoagulants are used in an anecdotal reports.

Surgical treatment

Indications for surgery include hypertension with critical renal artery stenosis, extremity claudication limiting activities of daily living, cerebrovascular ischaemia or critical stenoses of three or more cerebral vessels, moderate aortic regurgitation and cardiac ischaemia with confirmed coronary artery involvement.[58] In general, surgery is recommended at a time of quiescent disease to avoid complications, which include restenosis, anastamotic failure, thrombosis, haemorrhage, and infection.[58,73] Surgery may be unnecessary for aortic arch and splanchnic disease as a result of extensive collateral development.[72]

TA and Pregnancy

Because TA predominantly affects women of reproductive age, the issue of pregnancy is important. Fertility is not adversely affected, pregnancy per se does not appear to exacerbate the disease. Fetal outcome could be predicted on the basis of maternal vessel involvement (abdominal aorta and renal), severity of maternal hypertension, superimposed pre-eclampsia and timing of adequate blood pressure control. Abdominal aortic involvement and a delay in seeking medical attention predicted a poor perinatal outcome.

In one study, five pregnancies in their series of 60 patients, all of whom had normal deliveries of a normal live infant.[58] Only one patient had disease exacerbation during pregnancy.

Follow up

TA is a systemic vascular disease, which can progress and cause vital organ ischaemia; therefore long-term follow-up is recommended. The concept of remission in TA is not clear. Criteria for active disease were arbitrarily defined[74] and shown on table 6.

Table-VI

Criteria for active disease in patients with Takayasu's arteritis.

1	Systemic features (fever, musculoskeletal symptoms, etc.)
2	Elevated erythrocyte sedimentation rate
3	Features of vascular ischaemia or inflammation (claudication, vascular pain as carotodynia, diminished or absent pulse, vascular bruit), asymmetric blood pressure in either upper or lower limbs or both
4	Typical angiographic features

New onset or worsening of two or more features indicates "active disease".

As for clinical assessment of disease activity, methodologies vary. Most studies use the NIH criteria or the ITAS as disease activity scores. The ITAS showed a modest correlation with ESR in one study but no correlation with CRP.[83] Serological markers are not able to measure the activity of the disease. Better tools are required, in particular vascular imaging techniques with non-invasive methods are more appropriate. Doppler ultrasound is easily applied to extracranial vessels[75]. Angiography and CT cannot be routinely repeated due

to exposure to significant cumulative radiation. Moreover, FDG-PET scanning, detecting the presence of vascular inflammation and wall thickening, allows to assess the response to treatment during follow-up. Hopefully, in the future FDG-PET may become routinely performed in the detection and follow-up of TA.[76]

Prognosis

Long-term prognosis has been studied in a limited number of series of TA. Among the different series, mortality appears to range between 3%–15%. In one of the largest series with a long follow-up period, overall survival was much better than that in earlier series, with 97% at 10 and 86% at 15 years[77]. The restenosis rate after bypass procedures is also widely variable between 5% and 31%. Percutaneous transluminal angioplasty/ stenting has been reported to have a higher restenosis rate in the Indian cohort compared with the other reports (12%–71.4%).[78,79] 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 agents.[80-82] Disease phenotype and severity of disease expression, variations in access to modern investigations facilities, differences in medical and surgical therapy may result in different mortality rates.

Conclusion:

The management of patients with TA can be a challenge for the physician. There may be uncertainty with regard to the onset and course of the disease, a poor correlation between clinical assessment and disease activity, poor disease activity markers in blood, a lack of useful treatment in up to 25% of patients with progressive disease. Early diagnosis, followed by an aggressive treatment with glucocorticoids and immunosuppressive agents, may avoid rapid progression of the vascular lesions. Therapy should be started early at an aim of controlling disease activity and preserving vascular competence with minimal long-term side effects. Patients with a good prognosis should not be put at risk by treatments that are more harmful than the disease itself. There is a clear need to of further studies to explore the definitions of flare, remission, and response and aim to improve disease assessment tools with expert opinion and patient data.

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