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VASCULITIS (L ESPINOZA, SECTION EDITOR)

Takayasu Arteritis: Recent Developments

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Abstract

Purpose of Review Takayasu arteritis (TA) is a granulomatous inflammatory disorder that affects large vessels, especially aorta and its proximal branches. Its diagnosis can be extremely challenging due to the non-specificity of the systemic inflammatory manifestations during the early phase of the disease and usually follows an insidious clinical course until the emergence of vascular ischemic complications.

Recent Findings Its pathogenesis has been better delineated in recent years, especially the role of HLA-B*52 allele in certain ethnic groups, as well as the use of biological therapy, and surgical revascularization. Recent findings are discussed in depth.

Summary Clinical and epidemiological aspects of TA, recent developments in pathogenesis, and therapy are presented.

Keywords Vasculitis · Granulomatous disease · Biologic therapy · Aortitis · Surgical revascularization · Imaging studies

Introduction

Takayasu arteritis (TA) is a rare form of large vessel vasculitis, which involves preferentially the aorta and its proximal branches, and is most commonly seen in young Asian women. It was first described in 1905 by Mikito Takayasu in a young woman with ocular involvement, and Judge et al. in 1962 introduced the term Takayasu arteritis [1, 2]. This disorder is also recognized by other names, including pulseless disease, aortic arch syndrome, middle aortic syndrome, occlusive thromboaortopathy, and non-specific aortoarteritis. Its diagnosis can be challenging due to the non-specificity of clinical manifestations in the early phase of the disease and generally follows an insidious and chronic course until the appearance of ischemic manifestations that eventually lead the patient to seek medical attention.

Epidemiology

TA is a rare disorder, but has a worldwide distribution, although it appears to be more common in Asian populations, Central and South America, and less often in Caucasians and Black populations. Two epidemiologic studies, one from Japan, estimated the incidence of TA as 1–2 per million, while another study from West Asia, Kuwait, provided an incidence of 2.2 per million [3, 4]. Two recent studies from Turkey have reported incidence rates within the same range as those in Europe; the first study from western Turkey found an incidence of 1.1 per million, while the second study from northwestern Turkey found a relatively higher incidence as 3.4 per million, based on the population aged 16 and over [5, 6]. A lower annual incidence of 0.3 per million was reported in the UK in those aged less than 40 years [7]. An incidence of TA as 2.6 per million was reported from the USA (Olmsted County, MN, USA) [8].

A nationwide hospital-based study from Japan estimated the highest prevalence of TA at 40 per million, while a subsequent US study, published in abstract form, reported a low prevalence of 0.9 per million [9, 10]. A recently published study from southeast Norway reported 2–4 times higher population prevalence, 22.0 per million, than previously

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observed, with the highest prevalence found in Norwegians of Asian and African descent [11••].

Observed variations in incidence and prevalence for TA in different populations may be secondary to genetic, geographic, and methodological factors, and further studies are needed to elucidate them.

TA predominantly affects women, as clearly demonstrated in most of the published series around the world, although a less female predominance has been described in some other populations, including India and Israel [12, 13].

On the other hand, a firm association with the HLA-B*52 allele has long been established suggesting a strong genetic component in the pathogenesis of TA [14•]. Genetic factors, both within and outside the HLA region, were thoroughly examined in a recent review article, which concluded that HLA-B*52 is the only gene that shows an association with TA beyond ethnicity. Therefore, this data lends support to the notion that a higher prevalence of TA among Asians may be a reflection of higher allele frequency of HLA-B*52 in these populations [15].

Etiology and Pathogenesis

The etiology of TA remains to be elucidated, but strong circumstantial evidence suggest that in the presence of genetic predisposition, environmental triggers, microorganisms, commensal or pathogens, and/or their antigenic components triggers an immune response, in which pathogenic T cells and macrophages invade vessel walls, establish residency, and build autonomous, self-sufficient inflammatory lesions [16, 17•, 18, 19]. Pathogenic effector T cells invade and survive due to failed immune checkpoint inhibition [20•].

The arterial wall, a target of the immune reaction, is composed of vascular dendritic cells, endothelial cells, vascular smooth cells, and fibroblasts, which engage with activated T cells and macrophages leading eventually to luminal stenosis or aneurysmal wall damage of the vessel. This inflammatory process characteristically involves the inner wall and spares the outside of the blood vessels, progressing from a granulomatous inflammatory process (with infiltrating monocytes and lymphocytes) in the early stages, to a less obvious inflammatory reaction in advance stages of the disease in which adventitial fibrosis, smooth muscle proliferation in the intima, and vessel stenosis predominate.

A schematic representation of leading events in the pathogenesis is depicted in Fig. 1.

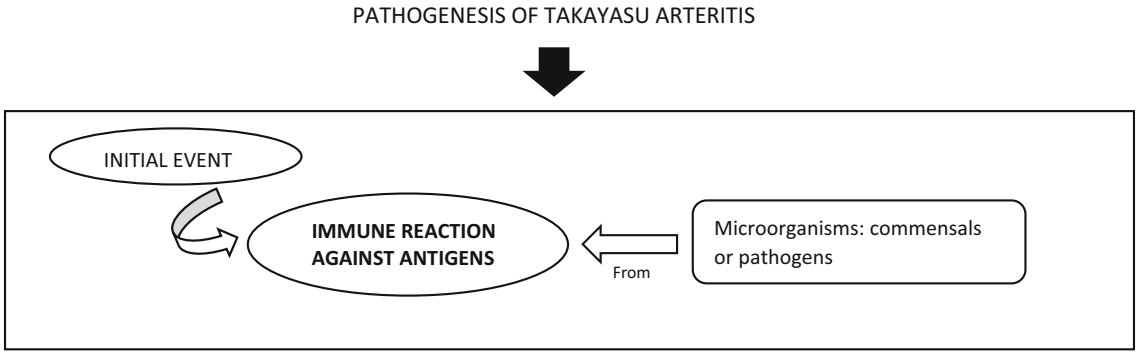
Evidence accumulated, thus far, supports an important role for autoimmune responses mediated by T cells, macrophages, dendritic cells, and others in the pathogenesis of TA. Patients with TA have been shown to have an increased number of circulating T cells with most of them exhibiting a state of activation, and a parallel decrease in the number of circulating Treg cells, a subtype of T cells essential to maintain homeostasis. On the other hand, B cells are not abundant in TA, but there is an increased number of antibodies produced by these cells (CD19+, CD20−, CD27) found in the blood of patients with TA, and CD20+ cells are present around the granulomas. Furthermore, a variety of pro-inflammatory cytokines such as IL-6, IL-8, IL-9, IL-17, and IL-18 are elevated in the serum of TA patients. Both elevated IL-6 and TNF-α correlate with disease activity, and they significantly decrease in response to biologic therapy, thus providing a rationale for their use in TA [16, 17•, 18, 19, 20•].

Other avenues of investigation are being explored including the potential role of the microbiota, circulating microparticles from endothelial cells, and immune cells, but further work is needed to establish a relationship [21, 22].

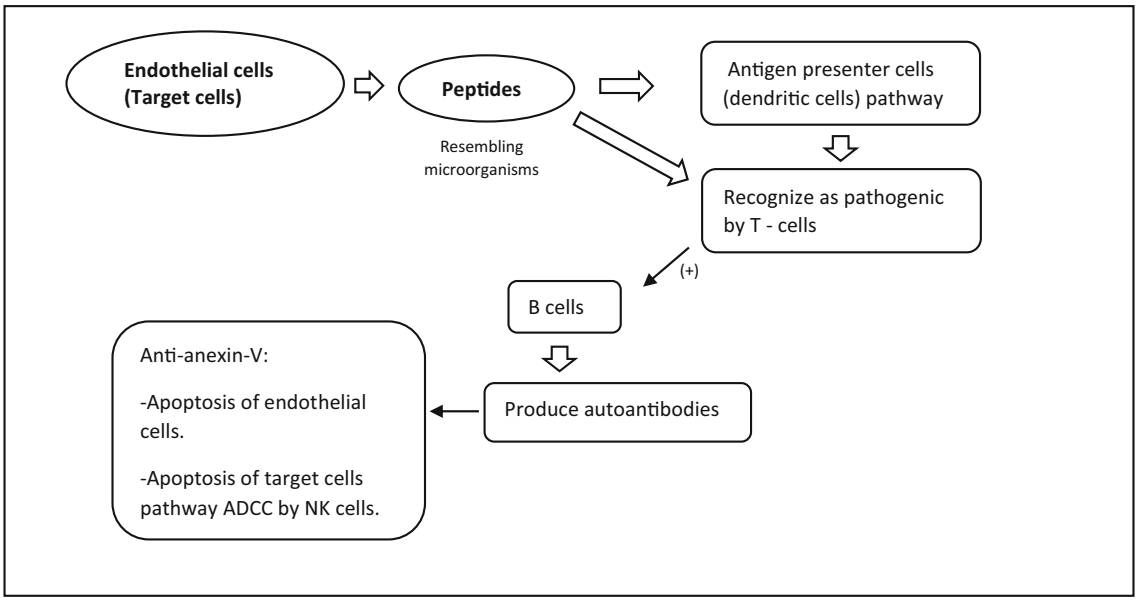
Fig. 1 Pathogenesis of Takayasu arteritis. **a** Peptides derived from endothelial cells (target cells), mimicking microorganism-derived peptides, through the antigen-presenting cell pathway (dendritic cells) are recognized as pathogenic by T cells, thus stimulating B cells to produce and release specific antibodies that react against the patient's own cells. In addition, anti-annexin V directly induces apoptosis of endothelial cells and could also trigger apoptosis by the cytotoxicity-dependent antibody pathway (ADCC) through NK cells. **b** Death of target cells can also be mediated by the NKGD/MICA interaction pathway. Immune cells that express the NKG2D receptor like the NK cells and gamma/delta T cells recognize the MICA ligand that is found in the target cells, thus inducing apoptosis. MICA can also be induced by microbes or their products. **c** The formation of tissue granuloma and fibrosis is due to persistent and repetitive activation of cells of the immune system and also from the release of pro-inflammatory cytokines. Persistently activated monocytes can differentiate into giant cells, which in turn promote inflammation at the vascular level, and eventually to fibrosis through the matrix metalloprotease pathway (MPPs), and TNF-α. Activation of other cells such as Th17 and NK cells also promote the formation of granuloma and fibrosis mediated by the release of cytokines. Sustained inflammatory response can also be mediated or spread by microbial components such as LPS that can induce the expression and activation of TLRs in dendritic cells and monocytes. IL-6, which is released by several immune cells and activated endothelial cells, plays an important role in maintaining the inflammatory process that eventually leads to fibrosis

Clinical Features

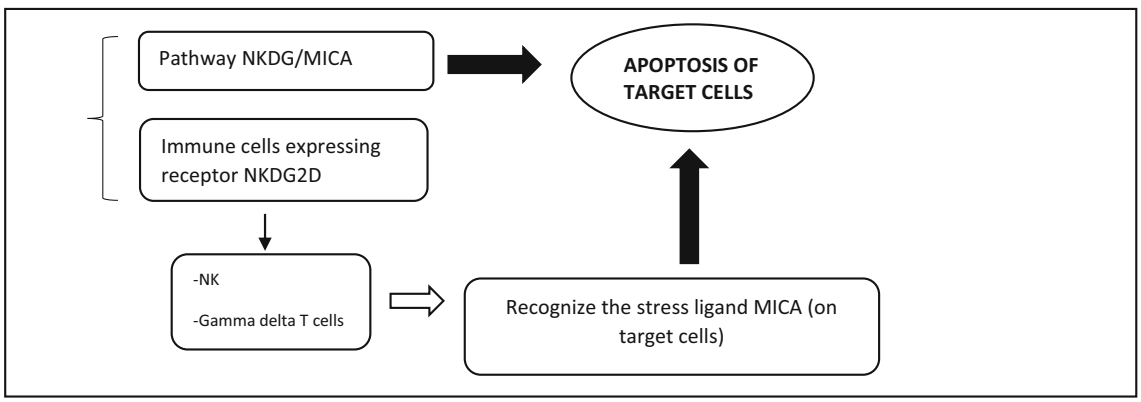
Most patients with TA exhibit an insidious, subacute clinical presentation, which leads to a delay in establishing an early diagnosis, and this may take months or even years. TA is characterized by a chronic, waxing, and waning clinical course that is for the most part dominated by non-specific constitutional and systemic symptoms in the early phase, and by vascular ischemic symptoms secondary to narrowing, occlusion, and dilation of the aorta and its main branches in late stages. Non-specific arthralgia and myalgia are present in 13–41% of patients, and they can be difficult to distinguish from the symptoms of other rheumatic disorders including


PATHOGENESIS OF TAKAYASU ARTERITIS
INITIAL EVENT
IMMUNE REACTION AGAINST ANTIGENS
From
Microorganisms: commensals or pathogens

a:


Endothelial cells (Target cells)
Peptides
Resembling microorganisms
Antigen presenter cells (dendritic cells) pathway
Recognize as pathogenic by T - cells
(+)
B cells
Produce autoantibodies
Anti-anexin-V:
-Apoptosis of endothelial cells.
-Apoptosis of target cells pathway ADCC by NK cells.

b:


Pathway NKDG/MICA
Immune cells expressing receptor NKDG2D
APOPTOSIS OF TARGET CELLS
-NK
-Gamma delta T cells
Recognize the stress ligand MICA (on target cells)

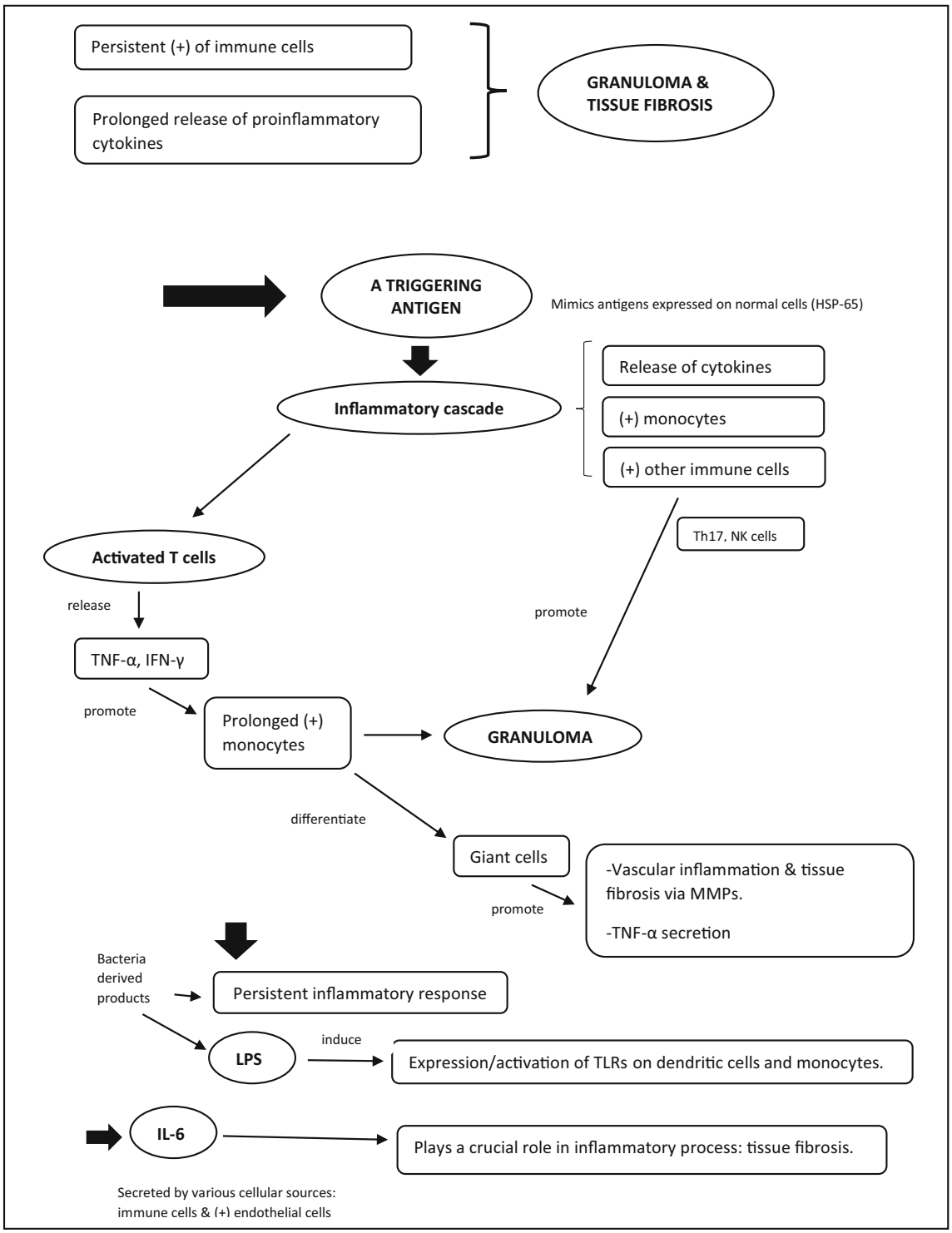


Fig. 1 (continued)

polymyalgia rheumatica, giant cell arteritis, and rheumatoid arthritis. Peripheral arthritis and sacroiliitis (11.9%) have been described in 19% of patients with TA. Transient ocular manifestations and vision loss can occur in 4–8% of patients with TA, but when present, they are typically associated with concomitant flow-limiting carotid or vertebral stenosis or occlusion. The presence of limb claudication, brachial pulse deficit, blood pressure discrepancy, and arterial bruits are critical characteristics for classifying patients with TA. Retinal involvement may occur in 14% of patients due to compromise

of the internal carotid circulation with central retinal hypoperfusion. Aortic regurgitation secondary to dilation of the aortic root occurs in 5–55% of patients. Coronary vessel stenosis may develop in 25% of patients. Pulmonary hypertension is not an uncommon occurrence in TA and has been described in about 10% of patients. Gender differences in the clinical presentation and vascular pattern in patients with TA have been described. Women appear to have a higher involvement of the supradiaphragmatic vessels, whereas in men, the abdominal vessels are more frequently affected. Renovascular hypertension secondary to arterial narrowing may also develop [23, 24, 25•].

Cutaneous involvement can occur in 3–28% of patients, and the most common lesions are erythema nodosum, pyoderma gangrenosum, erythema induratum, and ulcerative lesions. Inflammatory bowel disease may also occur in 2.6% of patients with TA [26•].

Diagnosis and Classification of Takayasu Arteritis

Ishikawa in Japan developed the first criteria for diagnosis of TA and included the mandatory criterion of age under 40 years; three major criteria: two of imaging and one clinical; and ten minor criteria: two clinical, one laboratory, and seven of imaging [27]. These criteria, however, had a severe limitation in that the control group consisted of 12 patients without evidence of vascular disorders. In addition, age of less than 40 years was severely criticized since it left out those patients with a possible diagnosis of late TA. Sharma et al. in 1996 from India subsequently updated Ishikawa's criteria by removing the mandatory criterion of age under 40; however, none of these two diagnostic criteria have been validated [28].

The most widely used and accepted criteria for TA is that of the American College of Rheumatology (ACR), which emerged in 1990 as a classification criteria, which includes five clinical criteria and one imaging criterion; these criteria were developed from comparing the clinical findings of 63 patients with TA with 744 controls with other vasculitic disorders [29].

Due to the complexity and heterogeneity of autoimmune disorders, there are few validated diagnostic criteria; therefore, the ACR has only validated the classification criteria so far for TA, and currently, the diagnosis of TA is based on the demographic, clinical characteristics, as well as laboratory results, histopathology, and imaging studies [30]. The classification criteria currently used do not consider those patients with age and symptomatology that starts between 40 and 50 years of age and also limits its usefulness in patients even older with vasculitis of large vessels in the absence of cranial symptoms. This makes difficult to distinguish late onset TA from giant cell arteritis.

Laboratory Findings

Laboratory investigation is not very helpful in TA. Findings generally reflect the underlying inflammatory process. Acute phase reactants, ESR and CRP, may be elevated. ESR (80%) rises more frequently than CRP (50%). Leukocytosis, mild normochromic normocytic anemia, thrombocytosis (may exceed 500,000/μl in patients with active disease), and hypergammaglobulinemia may be observed. Alterations in renal function are due to hypertension, and urinalysis and serum creatinine are usually normal. TA rarely causes glomerulonephritis.

Application of Imaging Techniques in Takayasu Arteritis and Disease Activity

Arterial wall damage and subsequent remodeling, as well as arterial stenosis or dilation, are crucial issues in TA. At present, non-invasive imaging techniques have emerged with great promise to improve the ability to identify both the extent and severity of the disease and to monitor its progress and clinical response to therapy [31, 32].

Angiography

Angiography remains the gold standard for the diagnosis of TA. It allows good images of the lumen of the vessels, although it does not detect changes in its walls. Six types of vascular involvement according to their arterial distribution have been described (Fig. 2). However, this technique presents limitations due to the inherent nature of invasiveness of the procedure, and because it does not provide the characteristics of the arterial wall. At present, its use is limited, and it is only used in specific indications such as preparation for arterial revascularization or measurement of central artery pressure in situations that it cannot be performed peripherally [33].

Positron Emission Tomography

Positron emission tomography (PET/CT) is widely used, highly sensitive, but expensive and requires exposure to radiation. It requires the use of 2-(F)-fluoro-2-deoxy-D-glucose (F-FDG), which is captured by metabolically active cells, mostly monocytes and macrophages, and determines the extent and severity of inflammation in the arterial wall in TA. The role of F-FDG-PET/CT in the follow-up of patients with TA is not clear yet. A meta-analysis of several TA studies showed that uptake of F-FDG had low sensitivity of 87% and specificity of 73% [34, 35••].

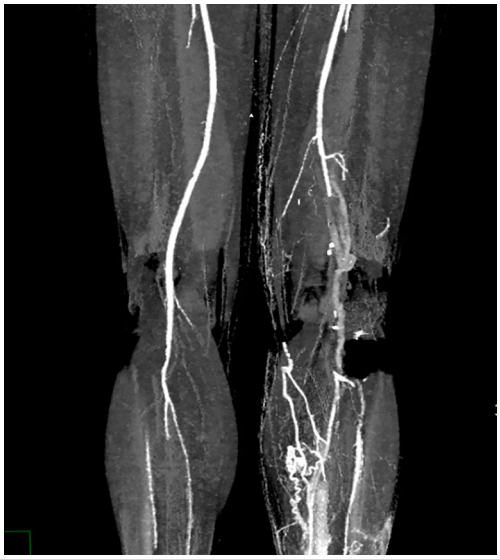


Fig. 2 Angio-CT of the left lower extremity of a 33-year-old man with TA. Aneurysmal dilatation of the common femoral artery, left superficial femoral artery, and left profunda. Apparent occlusion of the left lower extremity popliteal bypass graft. Left inguinal lymphadenopathy

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) allows the vascular tree to be extensively evaluated and it has become one of the most important techniques in TA. The lack of exposure to radiation is a major advantage, thus allowing multiple assessments, including its use in young patients. MR angiography (MRA) requires a short time and generates images of the arterial lumen [36, 37]. Specific MRA sequences can be performed without the use of contrast media, but limitations still exist and each sequence is applied to a specific arterial territory. MR can also evaluate the characteristics of the vessel wall, although it can take more time. Of late, MR and computed tomography (CT) have replaced angiography for the diagnosis of TA. The role of MR in differentiating disease activity remains controversial. Some medications may influence the results [38]. Currently, the main role of MR in TA is to provide a safe, non-invasive means to evaluate changes in the vascular anatomy over time. Recent studies combined non-invasive imaging studies with biomarkers in an effort to study both the role of biomarkers and the activity of the disease [39].

Computed Tomography

Computed tomography (CT) is also used to evaluate the lumen of the vessels and their walls, allowing a diagnosis in early phases of the disease long before the appearance of a significant decrease in the vessel lumen. In patients with TA, CT studies have developed an angiographic protocol: angio-CT, CTA. The appearance of a double ring, especially in the venous phase, can be observed after contrast uptake. The inner border represents the intima hyperplastic and the outer border the inflamed media and adventitia. The CTA provides an anatomical analysis similar to MR, and CTA is also capable of differentiating TA from atherosclerosis [40]. The advantages of CTA over MR include shorter examination time and more typical images than MR plus better anatomical details. CTA is particularly used preoperatively in cases in which revascularization is required. However, radiation exposure and the use of iodinated contrast media limit its long-term use. CTA also has the ability to assess coronary artery involvement in TA.

High-Resolution Ultrasound

High-resolution ultrasound (HRUS) is the most widely used technique in the management of patients with TA. This is based on its low cost, it is well tolerated, and it can distinguish the arterial wall of the lumen, performing the measurement of intima-media thickness (IMT) and delineate the degrees of stenosis or aneurysms. It has, however, limitations such as being operator-dependent and is limited to evaluating the vertebral and carotid circulation, the proximal and axillary subclavian arteries. It can, however, be used to evaluate the abdominal aorta in patients with TA. HRUS in patients with TA can reveal the presence of concentric thickening of the arterial wall that can often be bright due to active inflammation and edema [41, 42•, 43•]. The relationship, however, between the activity of the disease and the findings in the evaluation of the wall is not well established yet. But IMT has been shown to diminish in response to effective treatment.

At present, the use of imaging techniques has greatly improved diagnosis, management, and monitoring of patients with TA, but more studies are needed in order to ascertain activity of the disease, changes before and after immunosuppressive therapy, and its relationship with plasma biomarkers, as well as disease activity scores.

Recent Advances in the Management of Takayasu Arteritis

Challenges in the Assessment of Disease Activity and Arterial Wall Damage

Identification of the activity of the disease in TA remains of paramount importance. Distinguishing disease activity from damage (sequelae of previously active but currently inactive inflammation) in vasculitis is critical since active disease generally implies an intention to treat in an attempt to control the inflammatory process. The usually

used score from the National Institute of Health (NIH) is not validated, although it defines clinical remission (61% and 44% of patients exhibit angiographic and/or histological signs of activity or progression of disease respectively). There are available other activity scores that are not yet validated, including the Indian Takayasu Activity Score (ITAS) and the Disease Extent Index-Takayasu Arteritis (DEI-Tak) [44, 45, 46]. Due to a paucity of tools for the assessment of disease activity in LVV, the Outcome Measures in Rheumatology (OMERACT) Vasculitis working group recently identified domains that must be further evaluated for inclusion in a disease activity index in both TA and giant cell arteritis (GCA), while identifying a few discriminating items for use either in TA or GCA alone [47]. The evaluation of the activity and extension of the arterial involvement are essential to direct the treatment of TA. However, this issue remains a challenge, and the joint use of non-invasive imaging techniques, patient symptomatology, clinical findings, and acute phase reactants are currently needed to guide treatment [48].

Management of Takayasu Arteritis

Glucocorticoids (GC) remain the basis of initial treatment of TA, followed by the second-line agents or conventional immunosuppressive drugs such as methotrexate (MTX), azathioprine (AZA), mycophenolate mofetil (MMF), and leflunomide (LEF). Due to its adverse toxicity profile, cyclophosphamide (CYP) is only used in severe cases such as lung, retinal, or CVA. In the presence of refractory disease, the use of biologic agents including TNF inhibitors (TNFi), tocilizumab (TCZ), rituximab (RTX), and abatacept (ABA) has become the norm. When choosing the agent for the treatment of TA we are faced with two important issues, there is a low level of evidence and there are no accepted criteria of "active refractory disease," although the Turkish Takayasu Arteritis Group has made an attempt to define it (Fig. 3) [49, 50].

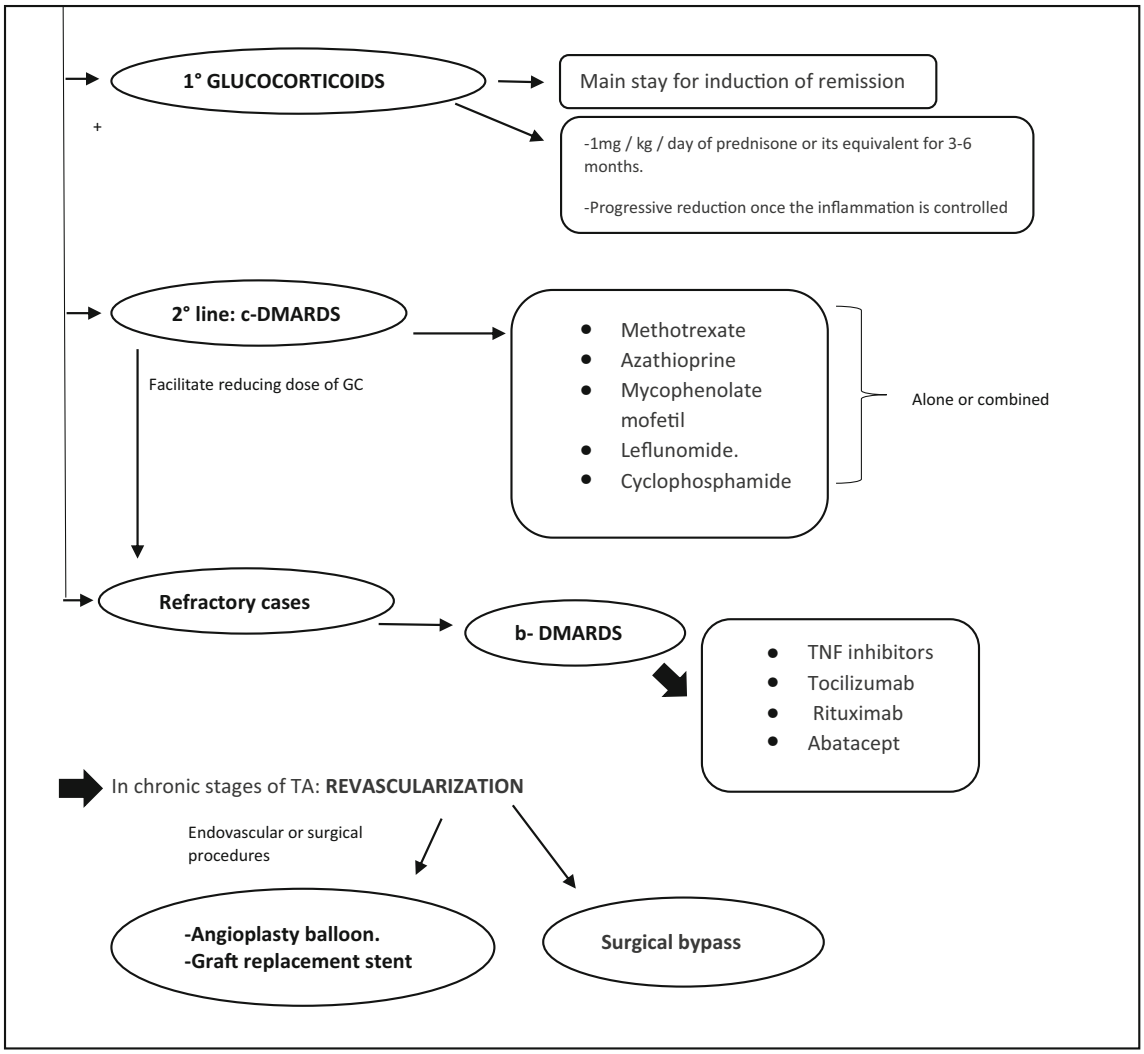


Fig. 3 Takayasu arteritis management

Glucocorticoids

Glucocorticoids (GCs) are the cornerstone for the induction of remission in TA. The usual starting dose is 1 mg/kg of prednisolone or its equivalent for 3 to 6 months, with progressive reduction once the inflammatory process is brought under control [51]. Recent data suggest that an initial dose of GC of 0.5 mg/kg/day along with a second-line agent such as MMF facilitates the reduction of GC and has a similar clinical response, without an increased risk of relapses [49]. Prevention of osteoporosis as well as other forms of GC toxicity such as diabetes mellitus, glaucoma, and cataracts must always be taken into consideration.

Conventional DMARDs

Conventional DMARDs (cDMARDs) are widely used in patients with TA in order to allow lower doses of GC; however, the evidence on its use is still scarce. Three retrospective series in India ($n = 21$), South America ($n = 10$), and Italy ($n = 3$) described the use of MMF 2 g/day in cases of refractory TA with a favorable clinical response and prompt decrease in the dose of GC and decrease in inflammatory biomarkers, but the duration of follow-up was short, and angiographic progression was not characterized (except in three Italian patients) [51, 52, 53]. The use of weekly oral MTX was described in a prospective series of 18 patients with TA, followed by a mean of 2.8 years, with favorable clinical responses, and retardation of angiographic progression in 13 patients, about half of whom GC could be tapered off, only to eventually relapse in the majority [54]. The efficacy of AZA, 2 mg/kg/day, in TA was demonstrated in a series of 15 patients with TA followed up for 1 year, with clinical resolution, and normalization of inflammatory markers in all, and with angiographic stabilization of disease [55]. Similar observation has been reported with the use of leflunomide, in which the authors concluded that following treatment with LEF of 15 patients with TA allows sustained remission in about half of patients in an average time of 12 months, and it was well tolerated by patients [56].

Biologic DMARDs

TNFi are the first-line biologic drugs in the treatment of TA. But among other options, tocilizumab (TCZ) has become a highly promising agent due to its mechanism of action. IL-6 plays an important role in the pathogenesis of TA, based on its elevated serum levels, and its correlation with disease activity, as well as the increase expression of IL-6 in vascular lesions, and genetic association of IL-6 and TA [57].

Biologic DMARDs (bDMARDs) are used in patients with persistently active disease despite the use of GC with or without cDMARDs. Two recent clinical trials have been published with bDMARDs in TA, one with Abatacept and another with Tocilizumab (TCZ). The results suggest that tocilizumab may decrease the rate of relapse in patients with TA. Abatacept therapy did not affect the rate of relapse in patients with TA [58, 59, 60].

Surgical Intervention

Revascularization of affected organs either through surgery or endovascular procedures, such as angioplasty balloon, stent, or graft replacement stents, constitutes the main treatment for the chronic phase of TA [61, 62, 63]. The success rate of endovascular intervention depends on the location, extent, and degree of arterial stenosis. In cases of stenosis in short segments, the use of the angioplasty balloon or the graft replacement stent may be useful. On the other hand, in cases of long segments with stenosis with a lot of fibrosis and occlusion, surgical bypass of the affected segment is associated with better results, especially in cases of compromised arteries in lower limbs and renal arteries [64]. In addition, the use of antiplatelet therapy should be taken into account, and although its use does not decrease the frequency of ischemic events in TA, it may reduce the risk of restenosis [63]. Therefore, 6 months of antiplatelet therapy is recommended, as well as post-surgical treatment with immunosuppressants to increase the rate of successful results.

Conclusion

Takayasu arteritis remains a rare disorder, with worldwide distribution but seen more frequently in Asian populations, probably related to HLA-B*52 allele. Its etiology is unknown, and its pathogenesis is complex and a result of environmental, genetic, and immunologic abnormalities. There has been a significant improvement in the use of imaging techniques on diagnosis, monitoring, and response to therapy, and newer biologic therapy appears highly promising. There remain a number of issues that need further investigation including the assessment of disease activity, differentiation TA activity from remission, better diagnostic and classification criteria, and selection of bDMARDs early in the disease.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Langford C. Takayasu arteritis. Rheumatology 7th Edition. 2019;14(165):1378–82.
2. Numano F, Okawara M, Inomata H, Kobaya-shi Y. Takayasu's arteritis. Lancet. 2000;356:1023–5.
3. Koide K. Takayasu arteritis in Japan. Heart Vessels Suppl. 1992;7: 48–54.
4. El-Reshaid K, Varro J, Al-Duwairi Q, Anim JT. Takayasu's arteritis in Kuwait. J Trop Med Hyg. 1995;98(5):299–305.
5. Birlik M, Kucukyavas Y, Aksu K, Solmaz D, Can G, Taylan A, et al. Epidemiology of Takayasu's arteritis in Turkey. Clin Exp Rheumatol. 2016;34(3 Suppl. 97):S33–9.
6. Saritas F, Donmez S, Direskeneli H, Pamuk ON. The epidemiology of Takayasu arteritis: a hospital-based study from northwestern part of Turkey. Rheumatol Int. 2016;36(7):911–6.
7. Watts R, Al-Taiar A, Mooney J, Scott D, Macgregor A. The epidemiology of Takayasu arteritis in the UK. Rheumatology. 2009;48: 1008–11.
8. Hall S, Barr W, Lie JT, Stanson AW, Kazmier FJ, Hunder GG. Takayasu arteritis. A study of 32 North American patients. Medicine (Baltimore). 1985;64(2):89–99.
9. Toshihiko N. Current status of large and small vessel vasculitis in Japan. Int J Cardiol. 1996;54(Suppl):S91–8.
10. Cotch MF, Hoffman GS. The prevalence, epidemiology and cost of hospitalizations for vasculitis in New York State: 1986 to 1990 [abstract]. Arthritis Rheum. 1995;38(Suppl. 9):S225.
11. •• Gudbrandsson B, Molberg O, Garen T, Palm O. Prevalence, incidence and disease characteristics of Takayasu arteritis differ by ethnic background; data from a large, population based cohort resident in Southern Norway. Arthritis Care Res (Hoboken). 2017;69: 278–85. **Good epidemioloc study decribing the prevalence and clinical characteristics of Takayasu arteritis in southeast Norway.**
12. Nooshin D, Neda P, Shahdokht S, Ali J. Ten- year investigation of clinical. Laboratory and radiologic manifestations and complications in patients with Takayasu's arteritis in three university hospitals. Malays J Med Sci. 2013;20(3):44–50.
13. Arnaud L, Haroche J, Limal N, Toledano D, Gambotti L, Costedoat Chalumeau N, et al. Takayasu arteritis in France: a single-center retrospective study of 82 cases comparing white, North African, and black patients. Medicine (Baltimore). 2010;89(1):1–17.
14. • Terao C. Revisited HLA and non-HLA genetics of Takayasu arteritis – where are we? J Hum Genet. 2016;61(1):27–32. **Data presented provide support for the notion that higher prevalence of TA among Asians may reflect higher allele frequency of HLA-B*52 in these populations.**
15. Takamura C, Ohhigashi H, Ebana Y, Isobe M. New human leukocyte antigen risk allele in Japanese patients with Takayasu arteritis. Circ J. 2012;76(7):1697–702.
16. Mirault T, Guillet H, Messas E. Immune response in Takayasu arteritis. Presse Med. 2017;46:e189–96.
17. • Espinoza JL, Ai S, Matsumura I. New insights on the pathogenesis of Takayasu arteritis: revisiting the microbial theory. Pathogens. 2018;7:73. https://doi.org/10.3390/pathogens7030073. **Concise review of pathogenic events in Takayasu arteritis.**
18. Kong X, Sun Y, Ma L, Chen H, Wei L, Wu W, et al. The critical role of IL-6 in the pathogenesis of Takayasu arteritis. Clin Exp Rheumatol. 2016;34:S21–7.
19. Tamura N, Maejima Y, Tezuka D, Takamura C, Yoshikawa S, Ashikaga T, et al. Profiles of serum cytokine levels in Takayasu arteritis patients: potential utility as biomarkers for monitoring disease activity. J Cardiol. 2017;70:278–85.
20. • Weyand CM, Watanabe R, Zhang H, Akiyama M, Berry GJ, Goronzy JJ. Cytokines, growth factors and proteases in medium and large vessel vasculitis. Clin Immunol. 2019. https://doi.org/10.1016/j.clim.2019.02.007. **Very good discussion of pathogenesis in medium and large vessel vasculitis.**
21. Talotta R, Atzeni F, Ditto MC, Gerardi MC, Sarzi-Puttini P. The microbiome in connective tissue and vasculitis: an updated narrative review. J Immunol Res. 2017;2017:6836498. https://doi.org/10.1155/2017/6836498.
22. Cheng X, Dang A, Lv N, Zhao T. Microparticles from endothelial cells and immune cells in patients with Takayasu arteritis. J Atheroscler Thromb. 2019;26:547–58.
23. Sanchez-Alvarez C, Mertz LE, Thomas CS, Cochuyt JJ, Abril A. Demographic, clinical, and radiologic characteristics of a cohort of patients with Takayasu arteritis. Am J Med. 2019;132:647–51.
24. Sari A, Sener YZ, Firat E, Armagan B, Erden A, Oksul M, et al. Pulmonary hypertension in Takayasu arteritis. Int J Rheum Dis. 2018;21:1634–9.
25. • Tomelleri A, Campochiaro C, Sartorelli S, Cavalli G, De Luca G, Baldissera E, et al. Gender differences in clinical presentation and vascular pattern in patients with Takayasu arteritis. Scand J Rheumatol. 2019;8:1–9. https://doi.org/10.1080/03009742.2019.1581838. **Interesting study demonstrating that gender has a strong influence on pattern of vascular involvement and also on clinical presentation in Takayasu arteritis.**
26. • Kwon OC, Lee SW, Park YB, Oh JS, Lee SH, Hong S, et al. Extravascular manifestations of Takayasu arteritis: focusing on the features shared with spondyloarthritis. Arthritis Res Ther. 2018;20:142. https://doi.org/10.1186/s13075-018-1643-7. **Interesting study demonstrating that up to 20% of patients with Takayasu arteritis may exhibit extravascular clinical manifestations.**
27. Ishikawa K. Diagnostic approach and proposed criteria for the clinical diagnosis of Takayasu's arteriopathy. J Am Coll Cardiol. 1988;12(4):964–72.
28. Sharma BK, Jain S, Suri S, Numano F. Diagnostic criteria for Takayasu arteritis. Int J Cardiol. 1996;54(Suppl):S141–7.
29. Arend WP, Michel BA, Bloch DA, Hunder GG, Calabrese LH, Edworthy SM, et al. The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis. Arthritis Rheum. 1990;33(8):1129–34.
30. Cui X, Qin F, Song L, Wang T, Geng B, Zhang W, et al. Novel biomarkers for the precise diagnosis and activity classification of Takayasu arteritis. Circ Genom Precis Med. 2019;12:e002080. https://doi.org/10.1161/CIRCGEN.117.002080.
31. Tombetti E, Mason J. Application of imaging techniques for Takayasu arteritis. Presse Med. 2017;46:e215–23.
32. Schmidt WA. Imaging in vasculitis. Best Pract Res Clin Rheumatol. 2013;27:107–18.
33. Russo RAG, Katsicas MM. Takayasu arteritis. Front Pediatr. 2018;6:265. https://doi.org/10.3389/fped.2018.00265.
34. Kobayashi Y, Ishii K, Oda K, Nariai T, Tanaka Y, Ishiwata K, et al. Aortic wall inflammation due to Takayasu arteritis imaged with 18F-FDG PET coregistered with enhanced CT. J Nucl Med. 2005;46:917–22.

35.•• Grayson PC, Alehashemi S, Bagheri AA, Cahid Civelek A, Cupps TR, Kaplan MJ, et al. Positron emission tomography as an imaging biomarker in a prospective, longitudinal cohort of patients with large vessel vasculitis. Arthritis Rheum. 2018;70:439–49. **Very good, prospective, longitudinal study of potential use of PET/CT as imaging biomarker in large vessel vasculitis.**

36. Miyazaki M, Akahane M. Non-contrast enhanced MR angiography: established techniques. J Magn Reson Imaging. 2012;35:1–19.

37. Wheaton AJ, Miyazaki M. Non-contrast enhanced MR angiography: physical principles. J Magn Reson Imaging. 2012;36:286–304.

38. Gotway MB, Araoz PA, Macedo TA, Stanson AW, Higgins CB, Ring EJ, et al. Imaging findings in Takayasu's arteritis. Am J Roentgenol. 2005;184:1945–50.

39. Jiang L, Li D, Yan F, Dai X, Li Y, Ma L. Evaluation of Takayasu arteritis activity by delayed contrast-enhanced magnetic resonance imaging. Int J Cardiol. 2012;155:262–7.

40. Zhu FP, Luo S, Wang ZJ, Jin ZY, Zhang LJ, Lu GM. Takayasu arteritis: imaging spectrum at multidetector CT angiography. Br J Radiol. 2012;85:e1282–92.

41. Schmidt WA. Technology insight: the role of color and power Doppler ultrasonography in rheumatology. Nat Clin Pract Rheumatol. 2007;3:35–42.

42.• Lottspeich C, Dechant C, Kohler A, Tischler M, Treitl KM, Treitl M, et al. Assessment of disease activity in Takayasu arteritis: potential role of contrast-enhanced ultrasound. Ultraschall Med. 2019. https://doi.org/10.1055/a-0817-5423. **Good study demonstrating the potential value of contrast-enhanced ultrasound in the assessment of disease activity in Takayasu arteritis.**

43.• Li Z, Zheng Z, Ding J, Li X, Zhao Y, Kang F, et al. Contrast-enhanced ultrasonography for monitoring arterial inflammation in Takayasu arteritis. J Rheumatol. 2019;46:616–22. **Interesting study demonstrating the value of contrast-enhanced ultrasound in the assessment of disease activity in Takayasu arteritis**.

44. Kerr GS, Hallahan CW, Giordano J, Leavitt RY, Fauci AS, Rottem M, et al. Takayasu arteritis. Ann Intern Med. 1994;120:919–29.

45. Misra R, Danda D, Rajappa SM, Ghosh A, Gupta R, Mahendranath KM, et al. Development and initial validation of the Indian Takayasu Clinical Activity Score. Rheumatology. 2013;52:1795–801.

46. Aydin SZ, Yilmaz N, Akar S, Aksu K, Kamali S, Yucel E, et al. Assessment of disease activity and progression in Takayasu's arteritis with Disease Extent Index-Takayasu. Rheumatology. 2010;49:1889–93.

47. Aydin SZ, Direskeneli H, Merkel PA. Assessment of disease activity in large-vessel vasculitis: results of an international Delphi exercise. J Rheumatol. 2017;44(12):1928–32.

48. Keser G, Aksu K. What is new in management of Takayasu arteritis? Presse Med. 2017;46:e229–35.

49. Goel R, Danda D, Joseph G, et al. Long-term outcome of 251 patients with Takayasu arteritis on combination immunosuppressant therapy: single centre experience from a large tertiary care teaching hospital in Southern India. Semin Arthritis Rheum. 2017;8(47):718–26.

50. Duru N, Van Der Goes MC, Jacobs JWG, et al. EULAR evidence-based and consensus-based recommendations on the management of medium to high-dose glucocorticoid therapy in rheumatic diseases. Ann Rheum Dis. 2013;72(12):1905–13.

51. Goel R, Danda D, Mathew J, Edwin N. Mycophenolate mofetil in Takayasu's arteritis. Clin Rheumatol. 2010;29(3):329–32.

52. Shinjo SK, Pereira RMR, Tizziani VAP, Radu AS, Levy-Neto M. Mycophenolate mofetil reduces disease activity and steroid dosage in Takayasu arteritis. Clin Rheumatol. 2007;26(11):1871–5.

53. Daina E, Schieppati A, Remuzzi G. Mycophenolate mofetil for the treatment of Takayasu arteritis: report of three cases. Ann Intern Med. 1999;130(5):422–6.

54. Hoffman GS, Leavitt RY, Kerr GS, Rottem M, Sneller MC, Fauci AS. Treatment of glucocorticoid-resistant or relapsing Takayasu arteritis with methotrexate. Arthritis Rheum. 1994;37(4):578–82.

55. Valsakumar AK, Valappil UC, Jorapur V, Garg N, Nityanand S, Sinha N. Role of immunosuppressive therapy on clinical, immunological, and angiographic outcome in active Takayasu's arteritis. J Rheumatol. 2003;30(8):1793–8.

56. de Souza AW, de Almeida AR, de Cinque AH, et al. Leflunomide in Takayasu arteritis – a long term observational study. Rev Bras Reumatol Engl Ed. 2016;56(4):371–5.

57. Kong X, Sun Y, Ma L, Chen H, Wei L, Wu W, et al. The critical role of IL-6 in the pathogenesis of Takayasu arteritis. Clin Exp Rheumatol. 2016;34(3 Suppl. 97):S21–7.

58. Langford CA, Cuthbertson D, Ytterberg SR, et al. A randomized, double-blind trial of abatacept (CTLA-4Ig) for the treatment of Takayasu arteritis. Arthritis Rheum. 2017; *l*;**69**(4):846–53.

59. Nakaoka Y, Isobe M, Takei S, Tanaka Y, Ishii T, Yokota S, et al. Efficacy and of tocilizumab in patients with refractory Takayasu arteritis: results from a randomised, double-blind, placebo- controlled, phase 3 trial in Japan (the TAKT study). Ann Rheum Dis. 2017;77(3):348–54.

60. Ferfar Y, Mirault T, Desbois AC, Comarmond C, Messas E, Savey L, et al. Biotherapies in large vessel vasculitis. Autoimmun Rev. 2016;15(6):544–51.

61. Saadoun D, Lambert M, Mirault T, Resche-Rigon M, Koskas F, Cluzel P, et al. Retrospective analysis of surgery versus endovascular intervention in Takayasu arteritis: a multicenter experience. Circulation. 2012;125:813–9.

62. Ham SW, Kumar SR, Rowe VL, Weaver FA. Disease progression after initial surgical intervention for Takayasu arteritis. J Vasc Surg. 2011;54:1345–51.

63. de Souza AWS, Machado NP, Pereira VM, Arraes AED, Reis Neto ET, Mariz HA, et al. Antiplatelet therapy for the prevention of arterial ischemic events in Takayasu arteritis. Circ J. 2010;74:1236–41.

64. Park MC, Lee SW, Park YB, Lee SK, Choi D, Shim WH. Postinterventional immunosuppressive treatment and vascular restenosis in Takayasu's arteritis. Rheumatology. 2006;45:600–5.