Giant Cell Arteritis versus Takayasu Arteritis: An Update

Pavlos Stamatis

Mediterr J Rheumatol 2020;31(2):174-82

E-ISSN: 2529-198X

MEDITERRANEAN JOURNAL OF RHEUMATOLOGY | 31 2 2020

VIEWPOINT

Giant Cell Arteritis versus Takayasu Arteritis: An Update

Pavlos Stamatis

Department of Clinical Sciences, Rheumatology, Lund University, Sweden

ABSTRACT

Giant cell arteritis (GCA) and Takayasu Arteritis (TAK) are two systemic granulomatous vasculitides affecting medium- and large-sized arteries. Similarities in GCA and TAK regarding the clinical presentation, the systemic inflammatory response and the distribution of the arterial lesions, have triggered a debate over the last decade about whether GCA and TAK represent two different diseases, or are age-associated different clinical phenotypes of the same disease. On the other hand, there are differences regarding epidemiology, several clinical features (eg, polymyalgia rheumatica in GCA) and treatment. The aim of this review is to present the latest data regarding this question and to shed some light on the differences and similarities between GCA and TAK regarding epidemiology, genetics, pathogenesis, histopathology, clinical presentation, imaging and treatment. The existing data in literature support the opinion that GCA and TAK are different clinical entities.

Mediterr J Rheumatol 2020;31(2):174-82

https://doi.org/10.31138/mjr.31.2.174

Article Submitted: 6 Dec 2019; Revised Form: 24 Feb 2020; Article Accepted: 03 Mar 2020; Available Online: 30 Jun 2020

Keywords: Giant cell arteritis, Takayasu arteritis, epidemiology, pathogenesis, histopathology, angiography

ABBREVIATIONS

ACR: American College of Rheumatology
AION: Anterior optic ischemic neuropathy
bDMARDs: Biologic disease-modifying anti-rheumatic drugs
CHCC: Chapel Hill consensus conference
CVA: Cerebrovascular accident
FDG-PET: Fluorodeoxyglucose-positron emission tomography
GCA: Giant cell arteritis
GCs: Glucocorticoids
HLA: Human leucocyte antigen
HSP-65: Heat shock protein 65 kDA
IL-17: Interleukin-17
IL-23: Interleukin-23
JAK-inhibitors: Janus kinase inhibitors
MICA: MHC class I polypeptide-related sequence A
MRA: Magnetic resonance angiography
NK cells: Natural killer cells
PMR: Polymyalgia rheumatica
sDMARDs: Synthetic disease-modifying anti-rheumatic drugs
SNP: Single nucleotide polymorphism
TAB: Temporal artery biopsy
TAK: Takayasu arteritis
Th1 cells: T helper type 1 cells
Th17 cells: T helper type 17 cells
TNF-α: Tumor necrosis factor alpha
Vas DCs: Vascular dendritic cells

Corresponding Author:
Pavlos Stamatis, MD
Department of Internal Medicine, Rheumatology Section
Lund University
SE-254 37 Helsingborg, Sweden
Tel.: +46 46 17 38 60
E-mail: pavlos.stamatis@med.lu.se

INTRODUCTION

Giant cell arteritis (GCA) and Takayasu Arteritis (TAK) are two systemic vasculitides with predominantly granulomatous infiltrates that affect the aorta and its main branches.

GCA and TAK comprise the group of large-vessel vasculitides. Traditionally, they are considered two different clinical entities. GCA and TAK are described both in the American College of Rheumatology 1990 classification criteria (ACR 1990) and in the 2012 Chapel Hill Consensus Conference definitions (2012 CHCC) as two different diseases.[1-3] In both sets of criteria, age is used as an important discriminator between GCA and TAK. However, both GCA and TAK share several common clinical, histopathological and imaging features. The last decade, there is an ongoing debate about whether GCA and TAK represent two different diseases, or the same disease.[4,5] Furthermore, regarding patients with large vessel vasculitis aged between 40-50 years of age, it is not always clear whether the large vessel involvement is due to late onset TAK or early onset GCA. The purpose of this article is to summarize the differences and common features between GCA and TAK with respect to epidemiology, pathogenesis, histopathology, clinical features, imaging, and treatment.

EPIDEMIOLOGY

GCA is the most common vasculitis affecting individuals aged ≥50 years.[6-8] The disease is very rare in individuals younger than 50 years of age. The mean age of disease onset is around the age of 75 years, in particular in patients with predominantly cranial symptoms.[7,9] However, patients with large vessel involvement are generally younger at the time of GCA diagnosis.[10,11] The disease is more common in Scandinavian populations and in populations with Scandinavian ancestry.[6,7] The incidence of the disease increases with increasing latitude, with higher incidence rates in North European countries and lower incidence rates in Mediterranean and Asiatic countries.[6,12-14] The incidence rate of biopsy-proven GCA (per 100.000 individuals ≥50 years) is 14.1 in Southern Sweden, 5.8 in Northern Italy and 1.1 in Turkey.[6,12,14] The ratio between females and males is almost 3:1 in Northern Europe, but significantly lower in Southern Europe and Asia.[6,7,14,15] A recent meta-analysis has shown that patients with GCA do not have increased long-term mortality in comparison with the background population.[16] However, a study from Southern Sweden has demonstrated increased mortality the first 2 years after the GCA diagnosis,[6] and the aforementioned meta-analysis has also demonstrated an increased mortality in hospitalized patients.[16] Additionally, GCA patients have an increased risk of death due to cardiovascular disease.[17]

The incidence rate of TAK is significantly lower in comparison with GCA. The incidence of the disease (overall population without age restriction per 1 million inhabitants) has been reported to be 1-2 in Japan, 2.2 in Kuwait, 1.1 in Turkey, 0.7 in Sweden, 0.4 in Denmark and 0.4-1 in Germany.[18-24] The incidence of the disease peaks in the 15-30 years-old age group.[22, 25-27] The female:male ratio has been reported to be 5:1 in Japan, and a higher ratio has been reported in Southern Sweden with 13:0 ratio.[19,22,27] In contrast to GCA, TAK is very common in individuals with Asiatic ancestry.[26] Mortality is approximately 3 times higher in patients with TAK in comparison with age- and gender-matched controls.[28,29] Caucasian race and smoking have been identified as risk factors associated with mortality.[28]

GENETIC FACTORS

Carmona et al. investigated the presence of genetic similarities between GCA and TAK in a meta-analysis of large-scale genotyping data.[30]

HLA-associations

Single nucleotide polymorphisms (SNPs) in genes in the Human Leucocyte Antigen (HLA) class II regions, and in particular in the region between HLA-DRA and HLA-DRB1, were associated with GCA.[31] On the other hand, SNPs in genes located in the regions of HLA class I, between HLA-B and MHC class I polypeptide-related sequence A; MICA, were associated with TAK.[30] Particularly, the HLA Bw52 gene has been associated with susceptibility for TAK not only in Japanese populations, but even in European and American populations.[25,32,33]

Non-HLA associations

Regarding SNPs outside the HLA-region, only one SNP was statistically significant affecting both GCA and TAK. This SNP was located in the region which encodes interleukin 12B (IL-12B).[30] The affected gene encodes the P40 subunit, the common subunit between IL-12 and IL-23.

Taken all together, with the exception of the association of the SNP outside the HLA-region, there is no significant genetic correlation between GCA and TAK. GCA is associated with genes located in the HLA II region, whereas TAK is associated with genes located in the HLA I region.

PATHOGENESIS

The above-mentioned HLA-class II genetic associations and the presence of clonal T-cells in different arterial sites suggest that GCA is an immune mediated disease.[34-36] In large and medium sized arteries with vasa vasorum (diameter ≥ 2000μm), reside in the adventitia media border vascular dendritic cells (vas DCs).[37] These vas DCs in healthy individuals are tolerogenic, sparing the host of the devastating consequences of inflammation in the arterial tissue.[36,37] Several studies have shown that these vas DCs are impaired in GCA.[36,38-40] In predisposed for GCA individuals, impaired vas DCs (eg, with polymorphisms in their Toll-like receptors) may be activated by the presence of danger signals, gaining T stimulatory capacity.[41-43] This activation causes the migration of these DCs in the media where DCs produce chemotactic factors, which, in turn,

cause the migration and activation of T-cells and macrophages.[36,37] The subsequent inflammatory cascade orchestrated, mainly, by Th1-cell mediated and Th17-cell mediated responses contribute to the granulomatous infiltrate seen in GCA.[37,44] There are also emerging data regarding possible immunostromal interactions (between T-cells, vascular smooth cells and endothelial cell, eg, Notch-Notch ligand interactions) and immunoinhibitory signals such as PD1-PDL1 pathway.[37,45,46]

The pathogenesis of TAK is poorly understood. Similarly to GCA, there is an inflammatory cascade initiated by impaired DCs and orchestrated by Th-1 and Th-17 responses resulting in the granulomatous infiltrate.[47] However, there are some differences between GCA and TAK. In TAK, a currently unknown stimulus causes the overexpression of heat shock protein 65 kDA (HSP-65) which causes, in turn, the expression of cell surface protein MICA on vascular cells.[48] MICA functions as a ligand for the NKG2D receptor, a receptor which is usually expressed in γδ T-cells, CD8-αβ T-cells and NK-cells.[49] The recognition of MICA by γδ T-cells and NK-cells results in the production of perforin with subsequent vascular inflammation and damage.[47] The dysregulated immune response and the uncontrolled activation of repair mechanisms contribute to the vascular damage seen in TAK.

A very interesting finding is that in patients with GCA who are treated with glucocorticoids (GCs), the level of circulating Th-17 cytokines is significantly reduced after the treatment, whereas the level of Th-1 cytokines is unaffected in patients with chronic disease.[38,45] The same statement stands even for the cellular populations of Th17 and Th1 cells in specimens of temporal artery biopsies (TABs) from patients with GCA.[44] On the contrary, in TAK, the level of Th1-related cytokines is reduced after the treatment, whereas the level of Th-17 cytokines is unaffected.[50]

HISTOPATHOLOGY

The TABs of patients with GCA show lymphocytic and/or granulomatous inflammation. Granulomatous inflammation may be present in the majority of TABs of patients with GCA.[51] Regarding the location of the inflammatory infiltrate, the most frequent pattern is the pattern of transmural inflammation (75%), with the inflammatory infiltrate crossing the external elastic lamina and extending to the media.[52] Inflammation in the media is the classical hallmark of GCA,[53] and the inflammatory bulk in GCA is typically located in the adventitia media border.[54] The inflammatory infiltrate usually consists of mature lymphocytes and macrophages. The macrophages are present in all arterial layers and may create rings along the internal elastic laminae.[55] Giant cells are usually located along the internal elastic laminae and are present in up to 75% of the positive biopsies.[51,53] The absence of multinucleated giant cells does not preclude the diagnosis of GCA. The granulomas in GCA are not usually compact/well formed. Plasma cells, eosinophils and neutrophils may also be present in various frequencies.[51,52] Neoangiogenesis and myofibroblastic proliferation of the intima are frequent findings.[52]

The histological features of TAK are often almost indistinguishable from GCA with lymphocytic infiltrates, with or without giant cells.[19] Multinucleated giant cells with engulfed fragmented elastic fibres may be observed in tunica media.[19] However, some subtle differences in TAK are the trend for more adventitial involvement and the compact/well-formed granulomas.[54] Severe adventitial scarring occurs more commonly in TAK.[26] In end-stage TAK, the aorta has macroscopically a lead-pipe-like appearance due to the extended fibrosis, calcifications and atherosclerosis.[19]

CLINICAL FEATURES

GCA is a heterogenous disease with 3 distinct clinical phenotypes, which may overlap with each other.[53] Patients with GCA may have the classical cranial GCA, large vessel GCA (LV GCA), isolated PMR, or an overlap between these 3 clinical phenotypes.[55] Headache of acute or subacute onset is present in approximately 70% of the cases as presenting symptom.[56-58] Constitutional symptoms may be present in approximately 50% of the cases,[57,59,60] whereas fever of unknown origin may be the presenting symptom in 10% of cases.[61] Polymyalgia rheumatica (PMR) is a cardinal symptom at the disease onset in 40% of the patients,[59,62-64] whereas 16-21% of patients with previously diagnosed PMR are going to develop GCA during their disease course.[55,65,66] PMR and headache are the most common symptoms when the disease flares.[53,56,67] One third of the GCA patients may have cranial ischemic symptoms at the time of GCA diagnosis (scalp tenderness and jaw claudication); symptoms which have been associated with severe ischemic complications such as stroke and visual loss.[56,60,64,68] Visual manifestations are present in approximately 20% of the patients.[69,70] However, the incidence of permanent visual loss has been reported to be reduced during the last decade probably due to the better recognition of the disease by clinicians.[71,72] Large vessel involvement may be present in 30%-83% of the patients at the onset of the disease, depending on the imaging modality which is used.[4,73,74] Finally, cerebrovascular accidents (CVAs), namely stroke and TIA, may occur early during the course of the disease, affecting most commonly the vertebrobasilar system in up to 7% of patients.[60,75-78] *Table 1* presents the most common presenting symptoms in GCA.

In TAK, there is often a pre-stenotic phase (inflammatory) where the only symptoms may be constitutional symptoms and elevated inflammatory markers.[79] If the carotid arteries are affected, carotidynia may be present at this stage due to the underlying inflammatory process.[80] The pre-stenotic phase is followed by the ischemic/

Table 1. Baseline symptoms in GCA, based on selected studies.

Study	Cases	Headache	Jaw claudication	Scalp tenderness	Visual symptoms	Constitutional symptoms	Arm claudication	PMR
Smith, 1983[67]	24	83%	25%	33%	33%	29%	NR	25%
Gonzalez-Gay, 2005[64]	240	84.6%	41%	34%	23%	61%	3%	40%
Schmidt, 2008[62]	176	64%	41%	NR	29%	NR	NR	43%
Zenone, 2013[60]	98	76%	35%	NR	15%**	46%	2%	31%
Tuckwell, 2017[56]	119	71.4%	32.8%	36.1%	5.1%**	NR	NR	43%
Pucelj, 2019[58]	169	71.6%	45%	NR	33.1%	69.2%	NR	14.2%

**Ischemia related vision loss, NR: not reported.

pulseless phase where arterial lesions (mainly stenosis and aneurysms) cause the signs and symptoms of the disease depending on the arteries which are affected.[79,81] Consequently, *cerebral ischemia* may be presented as dizziness, headache, vertigo and hemiplegia; *upper limp ischemia* may be presented as extremity claudication, absent/weak peripheral pulse, finger numbness, cold sensation and extremity pain; *pulmonary artery involvement* may be presented as dyspnoea and haemoptysis; *coronary artery involvement* may be presented as chest pressure, angina, palpitations, shortness of breath and arrythmia; *renal artery involvement* may be presented as hypertension[27,82]; *mesenteric artery involvement* may be presented as abdominal pain, diarrhoea and hemorrhage.[19,83] Some patients with TAK may develop skin manifestations such as erythema nodosum and pyoderma gangrenosum.[19,83] Eye manifestations may be present in TAK, but permanent visual loss is quite rare in TAK.[81] The eye manifestations in TAK may be caused by hypertensive arteriopathy, treatment-related cataracts, hypoperfusion secondary to cerebral ischemia, and retinal microaneurysms.[19,81,83] A recent meta-analysis showed that the pooled prevalence of CVAs in the TAK was 15.8%.[84] Finally, the need of surgical interventions in TAK is higher in comparison with GCA,[83] and there is a worse prognosis in patients with extended vascular involvement and complications.[82] *Table 2* illustrates the most common presenting symptoms in TAK.

IMAGING

Four recent studies have evaluated common features and differences between GCA and TAK regarding imaging. Furuta et al.[11] compared the clinical and radiographic findings in 22 patients with GCA and 23 patients with TAK. GCA patients were more likely to have headache, higher inflammatory response, previously diagnosed PMR and they were more likely to have long (>10 cm) tapered lesions in subclavian and carotid arteries. On the other side, TAK patients were younger, had longer diagnostic delay, had lesions in subdiaphragmatic

Table 2. Selected studies on Takayasu arteritis presenting symptoms.

Study	Country	Patients (n)	Constitutional Symptoms†	Upper limbs∞	Head and neck*	Eyes	Hypertension
Wong, 2018[107]	China	78	12%	18%	6%	1%	62%
Watanabe, 2015[108]	Japan	1372	41%	17.3%	22.6%	3.3%	4%
Kermani, 2015[10]	USA	125	33%	65%	45%	NR	39%
Mohammad, 2015[22]	Sweden	13	54%	46%	NR	8%	38%
Furuta, 2015[11]	UK	23	65%	74%	0%	4%	NR
Park, 2005[109]	Korea	108	64.8%	72.2	56.5%	NR	NR
Hall, 1985[110]	USA	32	44%	94%	NR	NR	41%

† At least one of the following symptoms: fever, asthenia, fatigue, weight loss.
∞ At least one of the following symptoms: pulselessness, vascular bruits, blood pressure difference, fatigue, coldness and numbness.
*At least one of the following symptoms: dizziness, vertigo, syncope, headache, carotidynia and masseter claudication.
NR: Not reported

arteries more frequently, and were more likely to have short non-tapered lesions in the carotid and subclavian arteries. Kermani et al.[10] compared the clinical and radiographic findings in 120 patients with LV GCA and 125 patients with TAK. Again, GCA patients had higher inflammatory markers at the baseline and TAK patients had longer diagnostic delay. Occlusive lesions in left subclavian artery were more likely to occur in TAK patients, whereas aneurysms in the thoracic aorta were more common in GCA patients. Stenotic/occlusive lesions in thoracic aorta were more common in patients with TAK. All the GCA patients in this study had radiographically proved large vessel involvement, but less than one third of these patients had clinically detectable upper extremity abnormalities. Although this study compares the clinical phenotype of GCA which resembles TAK the most, there are several clinical and radiographic differences between GCA and TAK. Gribbons et al.,[85] using a large multicentre multinational sample of 1068 patients with GCA and TAK, identified 6 patterns of arterial involvement, 3 patterns in GCA and 3 patterns in TAK. GCA patients were more likely to present: 1) low burden of the disease in large arteries (cluster four), 2) diffuse disease with involvement of the aorta and aortic arch (cluster five), and 3) axillary and subclavian disease (cluster six). On the other hand, patients with TAK were more likely to present: 1) involvement of abdominal, renal and mesenteric arteries (cluster one), 2) bilateral involvement of subclavian and carotid artery (cluster two), and 3) isolated involvement of left subclavian artery with minimal involvement of other arteries. Michailidou et al.,[80] in a prospective observational study, investigated the association of clinical symptoms with magnetic resonance angiography (MRA) and fluorodeoxyglucose-positron emission tomography (FDG-PET) pathology, and subsequently compared the results between MRA and FDG-PET. In GCA patients, the most common symptom was blurred vision (37%) and in TAK patient arm claudication (52%). Arm claudication, CVAs and carotidynia were more common in patients with TAK. Disease activity expressed as elevated FDG uptake in several arteries was higher in patients with GCA, whereas vascular damage expressed as structural changes in the MRA was higher in patients with TAK. The presence of carotidynia in patients with TAK was associated with carotid abnormalities in FDG-PET, reflecting the underlying inflammatory process. Of note, the absence of carotidynia does not preclude imaging abnormalities in the carotid arteries. None of the GCA patients reported carotidynia. Posterior headache in patients with GCA was associated with imaging abnormalities in vertebral arteries in both MRA and FDG-PET. *Table 3* presents demographic, clinical and radiographic features of GCA and TAK.

Table 3. Differential features between GCA and TAK. Based mainly on the studies of Grayson et al.[4], Furuta et al.[11], Kermani et al.[10], Carmona et al.[30] and Gribbons et al.[85]

Demographic, clinical and radiographic features	GCA	TAK
Young age at disease onset (≤40 years)	-	++
Asiatic ancestry	-	++
Association with genes in the HLA II region	++	-
Cranial symptoms	++	+
Constitutional symptoms	++	+
PMR	++	-
Aortic insufficiency murmur	-	++
Eye manifestations	++	-
Acute phase reactants	++	+
Sub-diaphragmatic arteries (mesenteric and renal)	-	++
Axillary arteries	++	+
Aortic wall thickening	++	+
Stenosis/occlusion	+	++
Long (≥10cm) tapered lesions	++	+
Response to TNF-α inhibitors	-	++
Surgery or endovascular intervention	-	+

++: very common, +: common, -: uncommon. GCA: Giant cell arteritis, TAK: Takayasu arteritis

TREATMENT

GCs remain the mainstay of treatment in GCA. The recent EULAR recommendations for the management of large vessel vasculitides advocate that the tapering of the GCs dose should reach to a target of 15-20 mg/day the first 3 months, and to a target dose below 5 mg/day after 1 year.[86] Of note, EULAR recommends the initiation of GC-tapering when remission is achieved.[86] In relapsing patients, in patients with life-threatening or organ-threatening manifestations, in patients with high future risk for glucocorticoid-related adverse events, and in patients where the prolonged use of GCs is expected to worsen pre-existing comorbidities, addition of a non-glucocorticoid immunosuppressive agent is recommended, including tocilizumab.[86,87] The aim of the addition of a non-glucocorticoid agent is not only to reduce the disease activity but also to reduce the cumulative dose of glucocorticoids. Regarding synthetic disease-modifying anti-rheumatic drugs (sDMARDs), a meta-analysis of 3 randomized controlled trials[88-90] has shown that addition of methotrexate is effective in patients with GCA reducing the risk for flares and having at the same time a significant GC-sparing effect.[91] In an observational study, leflunomide appears to be effective in the treatment of GCA as a GC-sparing agent.[92] Regarding biologic DMARDs, GIACTA trial has proved that weekly treatment with tocilizumab in combination with GCs reduces disease activity and has also a significant GC-sparing effect in comparison with treatment only with steroids.[93] Three randomized controlled trials on TNF-α inhibitors (infliximab, etanercept and adalimumab) have failed to show any effect and, thus, treatment with TNF-α inhibitors is not recommended in GCA.[94-96] There are ongoing phase 3 trials on abatacept (NCT02915159) and on the JAK-inhibitor upadacitinib (NCT03725202). With great interest, the METOGiA trial from the French vasculitis group is also much anticipated, where a head to head comparison of methotrexate and tocilizumab is planned (NTC03892785).

GCs remain also the mainstay of treatment in TAK. However, in TAK, the addition of a non-glucocorticoid agent such as methotrexate, azathioprine, leflunomide or mycophenolate mofetil is recommended at the time of diagnosis due to the high rate of relapse when patients receive monotherapy with GGs.[86,97-100] In relapsing and difficult to treat cases, addition of a TNF-α inhibitor or tocilizumab should be preferred.[86,99] An open-label trial[101] and several retrospective studies have demonstrated the efficacy of TNF-α inhibitors in TAK.[102-104] A recent randomized controlled trial of tocilizumab vs placebo failed to meet its primary outcome in the intention to treat analysis,[105] which was the time to relapse. However, the relapse-free survival was 51% in the tocilizumab group vs 23% in the placebo group, suggesting a favourable effect of tocilizumab. The recently presented, in the annual ACR meeting in Atlanta, ACR 2019 guidelines for the treatment of TAK recommended the use of TNF-α inhibitors as first line biologics in TAK, reserving tocilizumab for refractory to TNF-α cases (unpublished data). In a randomized double-blind trial of abatacept, the risk of relapse was not reduced, when abatacept was added in the treatment with GCs; thus, Abatacept is not recommended in patients with TAK.[106] The rate of vascular interventions is higher in TAK in comparison with GCA.[83] If possible, vascular interventions should be planned when disease activity is low.

CONCLUSION

Although inflammation of the aorta and its main branches is a common characteristic in both TAK and GCA, the existing data in literature support the opinion that TAK and GCA are two different diseases. There are striking differences in epidemiology (age, race), genetics (HLA II vs HLA I), histopathology (immune-cells comprising the infiltrate), clinical presentation (cranial symptoms and PMR in GCA), imaging (type of lesions and subdiaphragmatic involvement in TAK) and treatment (different responses in TNF-α inhibition).

CONFLICT OF INTEREST

The author declares no conflict of interest.

REFERENCES

1. Hunder GG, Bloch DA, Michel BA, Stevens MB, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum 1990;33:1122-8.
2. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised international chapel hill consensus conference nomenclature of vasculitides. Arthritis Rheum 2013;65:1-11.
3. 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;33:1129-34.
4. Grayson PC, Maksimowicz-McKinnon K, Clark TM, Tomasson G, Cuthbertson D, Carette S, et al. Distribution of arterial lesions in Takayasu's arteritis and giant cell arteritis. Ann Rheum Dis 2012;71:1329-34.
5. Maksimowicz-McKinnon K, Clark TM, Hoffman GS. Takayasu arteritis and giant cell arteritis: A spectrum within the same disease? Medicine 2009;88:221-6.
6. Mohammad AJ, Nilsson JA, Jacobsson LT, Merkel PA, Turesson C. Incidence and mortality rates of biopsy-proven giant cell arteritis in southern Sweden. Ann Rheum Dis 2015;74:993-7.
7. Brekke LK, Diamantopoulos AP, Fevang BT, Abetamus J, Espero E, Gjesdal CG. Incidence of giant cell arteritis in western Norway 1972-2012: A retrospective cohort study. Arthritis Res Ther 2017;19:278.
8. Crowson CS, Matteson EL. Contemporary prevalence estimates for giant cell arteritis and polymyalgia rheumatica, 2015. Semin Arthritis Rheum 2017;47:253-6.
9. Stamatis P, Turesson C, Willim M, Nilsson J-Å, Englund M, Mohammad AJ. Malignancies in giant cell arteritis: A population-based cohort study. J Rheumatol 2020 Mar;47(3):400-6.
10. Kermani TA, Crowson CS, Muratore F, Schmidt J, Matteson EL, Warrington KJ. Extra-cranial giant cell arteritis and Takayasu arteritis: How similar are they? Semin Arthritis Rheum 2015;44:724-8.

11. Furuta S, Cousins C, Chaudhry A, Jayne D. Clinical features and radiological findings in large vessel vasculitis: Are Takayasu arteritis and giant cell arteritis 2 different diseases or a single entity? J Rheumatol 2015;42:300.
12. Catanoso M, Macchioni P, Boiardi L, Muratore F, Restuccia G, Cavazza A, et al. Incidence, prevalence, and survival of biopsy-proven giant cell arteritis in northern Italy during a 26-year period. Arthritis Care Res (Hoboken) 2017;69:430-8.
13. Baldursson O, Steinsson K, Björnsson J, Lie JT. Giant cell arteritis in Iceland. An epidemiologic and histopathologic analysis. Arthritis Rheum 1994;37:1007-12.
14. Pamuk ON, Donmez S, Karahan B, Pamuk GE, Cakir N. Giant cell arteritis and polymyalgia rheumatica in northwestern Turkey: Clinical features and epidemiological data. Clin Exp Rheumatol 2009;27:830-3.
15. Bas-Lando M, Breuer GS, Berkun Y, Mates M, Sonnenblick M, Nesher G. The incidence of giant cell arteritis in Jerusalem over a 25-year period: Annual and seasonal fluctuations. Clin Exp Rheumatol 2007;25:S15-7.
16. Hill CL, Black RJ, Nossent JC, Ruediger C, Nguyen L, Ninan JV, et al. Risk of mortality in patients with giant cell arteritis: A systematic review and meta-analysis. Semin Arthritis Rheum 2017;46:513-9.
17. Lee YH, Song GG. Overall and cause-specific mortality in giant cell arteritis : A meta-analysis. Zeitschrift fur Rheumatologie 2018.
18. Koide K. Takayasu arteritis in Japan. Heart Vessels Suppl 1992;7:48-54.
19. Group JCSJW. Guideline for management of vasculitis syndrome (JCS 2008). Japanese circulation society. Circ J 2011;75:474-503.
20. el-Reshaid K, Varro J, al-Duwairi Q, Anim JT. Takayasu's arteritis in Kuwait. J Trop Med Hyg 1995;98:299-305.
21. 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:S33-9.
22. Mohammad AJ, Mandl T. Takayasu arteritis in southern Sweden. J Rheumatol 2015;42:853-8.
23. Dreyer L, Faurschou M, Baslund B. A population-based study of Takayasu's arteritis in eastern Denmark. Clin Exp Rheumatol 2011;29:S40-2.
24. Reinhold-Keller E, Herlyn K, Wagner-Bastmeyer R, Gross WL. Stable incidence of primary systemic vasculitides over five years: Results from the German vasculitis register. Arthritis Rheum 2005;53:93-9.
25. Karageorgaki ZT, Bertsias GK, Mavragani CP, Kritikos HD, Spyropoulou-Vlachou M, Drosos AA, et al. Takayasu arteritis: Epidemiological, clinical, and immunogenetic features in Greece. Clin Exp Rheumatol 2009;27:S33-9.
26. Kermani TA. Takayasu arteritis and giant cell arteritis: Are they a spectrum of the same disease? Int J Rheum Dis 2019;22 Suppl 1:41-8.
27. Watanabe Y, Miyata T, Tanemoto K. Current clinical features of new patients with Takayasu arteritis observed from cross-country research in japan: Age and sex specificity. Circulation 2015;132:1701-9.
28. Mirouse A, Biard L, Comarmond C, Lambert M, Mekinian A, Ferfar Y, et al. Overall survival and mortality risk factors in Takayasu's arteritis: A multicenter study of 318 patients. J Autoimmun 2019;96:35-9.
29. Schmidt J, Kermani TA, Bacani AK, Crowson CS, Cooper LT, Matteson EL, et al. Diagnostic features, treatment, and outcomes of Takayasu arteritis in a us cohort of 126 patients. Mayo Clin Proc 2013;88:822-30.
30. Carmona FD, Coit P, Saruhan-Direskeneli G, Hernandez-Rodriguez J, Cid MC, Solans R, et al. Analysis of the common genetic component of large-vessel vasculitides through a meta-immunochip strategy. Sci Rep 2017;7:43953.
31. Carmona FD, Mackie SL, Martín J-E, Taylor JC, Vaglio A, Eyre S, et al. A large-scale genetic analysis reveals a strong contribution of the hla class ii region to giant cell arteritis susceptibility. Am J Hum Genet 2015;96:565-80.
32. Terao C. Revisited HLA and non-HLA genetics of Takayasu arteritis—where are we? J Hum Genet 2016;61:27-32.
33. Soto ME, Vargas-Alarcon G, Cicero-Sabido R, Ramirez E, Alvarez-Leon E, Reyes PA. Comparison distribution of HLA-b alleles in Mexican patients with Takayasu arteritis and tuberculosis. Hum Immunol 2007;68:449-53.
34. Koster MJ, Warrington KJ. Giant cell arteritis: Pathogenic mechanisms and new potential therapeutic targets. BMC Rheumatol 2017;1:2.
35. Weyand CM, Liao YJ, Goronzy JJ. The immunopathology of giant cell arteritis: Diagnostic and therapeutic implications. J Neuroopthalmol 2012;32:259-65.
36. Ma-Krupa W, Jeon M-S, Spoerl S, Tedder TF, Goronzy JJ, Weyand CM. Activation of arterial wall dendritic cells and breakdown of self-tolerance in giant cell arteritis. J Exp Med 2004;199:173-83.
37. Weyand CM, Goronzy JJ. Immune mechanisms in medium and large-vessel vasculitis. Nat Rev Rheumatol 2013;9:731-40.
38. Weyand CM, Ma-Krupa W, Pryshchep O, Groschel S, Bernardino R, Goronzy JJ. Vascular dendritic cells in giant cell arteritis. Ann N Y Acad Sci 2005;1062:195-208.
39. Ciccia F, Rizzo A, Ferrante A, Guggino G, Croci S, Cavazza A, et al. New insights into the pathogenesis of giant cell arteritis. Autoimmun Rev 2017;16:675-83.
40. Wagner AD, Wittkop U, Prahst A, Schmidt WA, Gromnica-Ihle E, Vorpahl K, et al. Dendritic cells co-localize with activated cd4+ t cells in giant cell arteritis. Clin Exp Rheumatol 2003;21:185-92.
41. Deng J, Ma-Krupa W, Gewirtz AT, Younge BR, Goronzy JJ, Weyand CM. Toll-like receptors 4 and 5 induce distinct types of vasculitis. Circ Res 2009;104:488-95.
42. Song GG, Choi SJ, Ji JD, Lee YH. Toll-like receptor polymorphisms and vasculitis susceptibility: Meta-analysis and systematic review. Mol Biol Rep 2013;40:1315-23.
43. Álvarez Rodríguez L, López-Hoyos M, Mata C, Fontalba A, Calvo Alen J, Marín MJ, et al. Expression and function of toll-like receptors in peripheral blood mononuclear cells of patients with polymyalgia rheumatica and giant cell arteritis. Ann Rheum Dis 2011;70:1677.
44. Deng J, Younge BR, Olshen RA, Goronzy JJ, Weyand CM, Deng J, et al. Th17 and th1 t-cell responses in giant cell arteritis. Circulation 2010;121:906-15.
45. Weyand CM, Berry GJ, Goronzy JJ. The immunoinhibitory pd-1/pd-l1 pathway in inflammatory blood vessel disease. J Leukoc Biol 2018;103:565-75.
46. Watanabe R, Zhang H, Berry G, Goronzy JJ, Weyand CM. Immune checkpoint dysfunction in large and medium vessel vasculitis. Am J Physiol Heart Circ Physiol 2017;312:H1052-h9.
47. Marie I, Audeguy P, Francois A, F DEK, Richard C. Giant cell arteritis presenting as a breast lesion: Report of a case and review of the literature. Am J Med Sci 2008;335:489-91.
48. Arnaud L, Haroche J, Mathian A, Gorochov G, Amoura Z. Pathogenesis of Takayasu's arteritis: A 2011 update. Autoimmun Rev 2011;11:61-7.
49. Bauer S, Groh V, Wu J, Steinle A, Phillips JH, Lanier LL, et al. Activation of nk cells and t cells by nkg2d, a receptor for stress-inducible mica. Science 1999;285:727.
50. Saadoun D, Garrido M, Comarmond C, Desbois AC, Domont F, Savey L, et al. Th1 and th17 cytokines drive inflammation in Takayasu arteritis. Arthritis Rheum (Hoboken, NJ) 2015;67:1353-60.
51. Maleszewski JJ, Younge BR, Fritzlen JT, Hunder GG, Goronzy JJ, Warrington KJ, et al. Clinical and pathological evolution of giant cell arteritis: A prospective study of follow-up temporal artery biopsies in 40 treated patients. Mod Pathol 2017;30:788-96.
52. Cavazza A, Muratore F, Boiardi L, Restuccia G, Pipitone N, Pazzola G, et al. Inflamed temporal artery: Histologic findings in 354 biopsies, with clinical correlations. Am J Surg Pathol 2014;38:1360-70.
53. Restuccia G, Boiardi L, Cavazza A, Catanoso M, Macchioni P, Muratore F, et al. Flares in biopsy-proven giant cell arteritis in northern italy: Characteristics and predictors in a long-term follow-up study. Medicine 2016;95:e3524.

54. Stone JR, Bruneval P, Angelini A, Bartoloni G, Basso C, Batoroeva L, et al. Consensus statement on surgical pathology of the aorta from the society for cardiovascular pathology and the association for european cardiovascular pathology: I. Inflammatory diseases. Cardiovasc Pathol 2015;24:267-78.
55. Dejaco C, Duftner C, Buttgereit F, Matteson EL, Dasgupta B. The spectrum of giant cell arteritis and polymyalgia rheumatica: Revisiting the concept of the disease. Rheumatology (Oxford, England) 2017;56:506-15.
56. Tuckwell K, Collinson N, Dimonaco S, Klearman M, Blockmans D, Brouwer E, et al. Newly diagnosed vs. Relapsing giant cell arteritis: Baseline data from the giacta trial. Semin Arthritis Rheum 2017;46:657-64.
57. Grossman C, Barshack I, Koren-Morag N, Ben-Zvi I, Bornstein G. Baseline clinical predictors of an ultimate giant cell arteritis diagnosis in patients referred to temporal artery biopsy. Clin Rheumatol 2016;35:1817-22.
58. Pucelj NP, Hočevar A, Ješe R, Rotar Ž, Hawlina M, Fakin A, et al. The incidence of giant cell arteritis in slovenia. Clin Rheumatol 2019;38:285-90.
59. Alba MA, Garcia-Martinez A, Prieto-Gonzalez S, Tavera-Bahillo I, Corbera-Bellalta M, Planas-Rigol E, et al. Relapses in patients with giant cell arteritis: Prevalence, characteristics, and associated clinical findings in a longitudinally followed cohort of 106 patients. Medicine 2014;93:194-201.
60. Zenone T, Puget M. Characteristics of cerebrovascular accidents at time of diagnosis in a series of 98 patients with giant cell arteritis. Rheumatol Int 2013;33:3017-23.
61. Calamia KT, Hunder GG. Giant cell arteritis (temporal arteritis) presenting as fever of undetermined origin. Arthritis Rheum 1981;24:1414-8.
62. Schmidt WA, Seifert A, Gromnica-Ihle E, Krause A, Natusch A. Ultrasound of proximal upper extremity arteries to increase the diagnostic yield in large-vessel giant cell arteritis. Rheumatology (Oxford, England) 2008;47:96-101.
63. Brack A, Martinez-Taboada V, Stanson A, Goronzy JJ, Weyand CM. Disease pattern in cranial and large-vessel giant cell arteritis. Arthritis Rheum 1999;42:311-7.
64. Gonzalez-Gay MA, Barros S, Lopez-Diaz MJ, Garcia-Porrua C, Sanchez-Andrade A, Llorca J. Giant cell arteritis: Disease patterns of clinical presentation in a series of 240 patients. Medicine 2005;84:269-76.
65. Salvarani C, Gabriel SE, O'Fallon WM, Hunder GG. Epidemiology of polymyalgia rheumatica in Olmsted County, Minnesota, 1970-1991. Arthritis Rheum 1995;38:369-73.
66. Franzen P, Sutinen S, von Knorring J. Giant cell arteritis and polymyalgia rheumatica in a region of Finland: An epidemiologic, clinical and pathologic study, 1984-1988. J Rheumatol 1992;19:273-6.
67. Labarca C, Koster MJ, Crowson CS, Makol A, Ytterberg SR, Matteson EL, et al. Predictors of relapse and treatment outcomes in biopsy-proven giant cell arteritis: A retrospective cohort study. Rheumatology (Oxford, England) 2016;55:347-56.
68. Smith CA, Fidler WJ, Pinals RS. The epidemiology of giant cell arteritis. Report of a ten-year study in Shelby County, Tennessee. Arthritis Rheum 1983;26:1214-9.
69. Salvarani C, Cimino L, Macchioni P, Consonni D, Cantini F, Bajocchi G, et al. Risk factors for visual loss in an Italian population-based cohort of patients with giant cell arteritis. Arthritis Rheum 2005;53:293-7.
70. Gonzalez-Gay MA, Garcia-Porrua C, Llorca J, Hajeer AH, Branas F, Dababneh A, et al. Visual manifestations of giant cell arteritis. Trends and clinical spectrum in 161 patients. Medicine 2000;79:283-92.
71. Singh AG, Kermani TA, Crowson CS, Weyand CM, Matteson EL, Warrington KJ. Visual manifestations in giant cell arteritis: Trend over 5 decades in a population-based cohort. J Rheumatol 2015;42:309-15.
72. Saleh M, Turesson C, Englund M, Merkel PA, Mohammad AJ. Visual complications in patients with biopsy-proven giant cell arteritis: A population-based study. J Rheumatol 2016;43:1559-65.
73. Blockmans D, de Ceuninck L, Vanderschueren S, Knockaert D, Mortelmans L, Bobbaers H. Repetitive 18f-fluorodeoxyglucose positron emission tomography in giant cell arteritis: A prospective study of 35 patients. Arthritis Rheum 2006;55:131-7.
74. Prieto-Gonzalez S, Arguis P, Garcia-Martinez A, Espigol-Frigole G, Tavera-Bahillo I, Butjosa M, et al. Large vessel involvement in biopsy-proven giant cell arteritis: Prospective study in 40 newly diagnosed patients using ct angiography. Ann Rheum Dis 2012;71:1170-6.
75. Soriano A, Muratore F, Pipitone N, Boiardi L, Cimino L, Salvarani C. Visual loss and other cranial ischaemic complications in giant cell arteritis. Nat Rev Rheumatol 2017;13:476-84.
76. de Boysson H, Liozon E, Lariviere D, Samson M, Parienti JJ, Boutemy J, et al. Giant cell arteritis-related stroke: A retrospective multicenter case-control study. J Rheumatol 2017;44:297-303.
77. Samson M, Jacquin A, Audia S, Daubail B, Devilliers H, Petrella T, et al. Stroke associated with giant cell arteritis: A population-based study. J Neurol Neurosurg Psychiatry 2015;86:216-21.
78. Pego-Reigosa R, Garcia-Porrua C, Pineiro A, Dierssen T, Llorca J, Gonzalez-Gay MA. Predictors of cerebrovascular accidents in giant cell arteritis in a defined population. Clin Exp Rheumatol 2004;22:S13-7.
79. Mason JC. Takayasu arteritis--advances in diagnosis and management. Nat Rev Rheumatol 2010;6:406-15.
80. Michailidou D, Rosenblum JS, Rimland CA, Marko J, Ahlman MA, Grayson PC. Clinical symptoms and associated vascular imaging findings in Takayasu's arteritis compared to giant cell arteritis. Ann Rheum Dis 2020 Feb;79(2):262-7.
81. Muratore F, Basu N, Pipitone N. Takayasu's arteritis. EULAR online course on CTD; 2017.
82. Águeda AF, Monti S, Luqmani RA, Buttgereit F, Cid M, Dasgupta B, et al. Management of Takayasu arteritis: A systematic literature review informing the 2018 update of the EULAR recommendation for the management of large vessel vasculitis. RMD Open 2019;5:e001020-e.
83. Ponte C, Agueda AF, Luqmani RA. Clinical features and structured clinical evaluation of vasculitis. Best Pract Res Clin Rheumatol 2018;32:31-51.
84. Duarte MM, Geraldes R, Sousa R, Alarcao J, Costa J. Stroke and transient ischemic attack in Takayasu's arteritis: A systematic review and meta-analysis. J Stroke Cerebrovasc Dis 2016;25:781-91.
85. Gribbons KB, Ponte C, Carette S, Craven A, Cuthbertson D, Hoffman GS, et al. Patterns of arterial disease in Takayasu's arteritis and giant cell arteritis. Arthritis Care Res (Hoboken) 2019.
86. Hellmich B, Agueda A, Monti S, Buttgereit F, de Boysson H, Brouwer E, et al. 2018 update of the EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis 2020;79:19.
87. Turesson C, Börjesson O, Larsson K, Mohammad AJ, Knight A. Swedish society of Rheumatology 2018 guidelines for investigation, treatment, and follow-up of giant cell arteritis. Scand J Rheumatol 2019;48:259-65.
88. Hoffman GS, Cid MC, Hellmann DB, Guillevin L, Stone JH, Schousboe J, et al. A multicenter, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis. Arthritis Rheum 2002;46:1309-18.
89. Jover JA, Hernández-García C, Morado IC, Vargas E, Bañares A, Fernández-Gutiérrez B. Combined treatment of giant-cell arteritis with methotrexate and prednisone. A randomized, double-blind, placebo-controlled trial. Ann Int Med 2001;134:106-14.
90. Spiera RF, Mitnick HJ, Kupersmith M, Richmond M, Spiera H, Peterson MG, et al. A prospective, double-blind, randomized, placebo controlled trial of methotrexate in the treatment of giant cell arteritis (GCA). Clin Exp Rheumatol 2001;19:495-501.
91. Mahr AD, Jover JA, Spiera RF, Hernandez-Garcia C, Fernandez-Gutierrez B, Lavalley MP, et al. Adjunctive methotrexate for treatment of giant cell arteritis: An individual patient data meta-analysis. Arthritis Rheum 2007;56:2789-97.

92. Diamantopoulos AP, Hetland H, Myklebust G. Leflunomide as a corticosteroid-sparing agent in giant cell arteritis and polymyalgia rheumatica: A case series. BioMed Res Int 2013;2013:120638.
93. Stone JH, Tuckwell K, Dimonaco S, Klearman M, Aringer M, Blockmans D, et al. Trial of tocilizumab in giant-cell arteritis. N Engl J Med 2017;377:317-28.
94. Hoffman GS, Cid MC, Rendt-Zagar KE, Merkel PA, Weyand CM, Stone JH, et al. Infliximab for maintenance of glucocorticosteroid-induced remission of giant cell arteritis: A randomized trial. Ann Int Med 2007;146:621-30.
95. Martínez-Taboada VM, Rodríguez-Valverde V, Carreño L, López-Longo J, Figueroa M, Belzunegui J, et al. A double-blind placebo controlled trial of etanercept in patients with giant cell arteritis and corticosteroid side effects. Ann Rheum Dis 2008;67:625-30.
96. Seror R, Baron G, Hachulla E, Debandt M, Larroche C, Puéchal X, et al. Adalimumab for steroid sparing in patients with giant-cell arteritis: Results of a multicentre randomised controlled trial. Ann Rheum Dis 2014;73:2074-81.
97. Comarmond C, Biard L, Lambert M, Mekinian A, Ferfar Y, Kahn JE, et al. Long-term outcomes and prognostic factors of complications in Takayasu arteritis: A multicenter study of 318 patients. Circulation 2017;136:1114-22.
98. Ohigashi H, Haraguchi G, Konishi M, Tezuka D, Kamiishi T, Ishihara T, et al. Improved prognosis of Takayasu arteritis over the past decade--comprehensive analysis of 106 patients. Circ J 2012;76:1004-11.
99. Hellmich B, Agueda A, Monti S, Buttgereit F, de Boysson H, Brouwer E, et al. 2018 update of the EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis 2020 Jan;79(1):19-30.
100. Barra L, Yang G, Pagnoux C. Non-glucocorticoid drugs for the treatment of Takayasu's arteritis: A systematic review and meta-analysis. Autoimmun Rev 2018;17:683-93.
101. Hoffman GS, Merkel PA, Brasington RD, Lenschow DJ, Liang P. Anti-tumor necrosis factor therapy in patients with difficult to treat Takayasu arteritis. Arthritis Rheum 2004;50:2296-304.
102. Ohigashi H, Tamura N, Ebana Y, Harigai M, Maejima Y, Ashikaga T, et al. Effects of immunosuppressive and biological agents on refractory Takayasu arteritis patients unresponsive to glucocorticoid treatment. J Cardiol 2017;69:774-8.
103. Serra R, Butrico L, Fugetto F, Chibireva MD, Malva A, De Caridi G, et al. Updates in pathophysiology, diagnosis and management of Takayasu arteritis. Ann Vasc Surg 2016;35:210-25.
104. Gudbrandsson B, Molberg Ø, Palm Ø. Tnf inhibitors appear to inhibit disease progression and improve outcome in Takayasu arteritis; an observational, population-based time trend study. Arthritis Res Ther 2017;19:99.
105. Nakaoka Y, Isobe M, Takei S, Tanaka Y, Ishii T, Yokota S, et al. Efficacy and safety 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 2018;77:348-54.
106. Langford CA, Cuthbertson D, Ytterberg SR, Khalidi N, Monach PA, Carette S, et al. A randomized, double-blind trial of abatacept (ctla-4ig) for the treatment of Takayasu arteritis. Arthritis Rheumatol (Hoboken, NJ) 2017;69:846-53.
107. Wong SPY, Mok CC, Lau CS, Yip ML, Tam LS, Ying KY, et al. Clinical presentation, treatment and outcome of Takayasu's arteritis in southern chinese: A multicenter retrospective study. Rheumatol Int 2018;38:2263-70.
108. Watanabe Y, Miyata T, Tanemoto K. Current clinical features of new patients with Takayasu arteritis observed from cross-country research in Japan: Age and sex specificity. Circulation 2015;132:1701-9.
109. Park MC, Lee SW, Park YB, Chung NS, Lee SK. Clinical characteristics and outcomes of Takayasu's arteritis: Analysis of 108 patients using standardized criteria for diagnosis, activity assessment, and angiographic classification. Scand J Rheumatol 2005;34:284-92.
110. Hall S, Barr W, Lie JT, Stanson AW, Kazmier FJ, Hunder GG. Takayasu arteritis. A study of 32 North American patients. Medicine 1985;64:89-99.