Large-vessel vasculitis

Patrice Cacoub*, Matheus Vieira*, Carol A Langford, Zoubida Tazi Mezalek, David Saadoun

Primary large-vessel vasculitis encompasses conditions that, despite sharing many common features, constitute distinct entities that have their own prognostic implications. These conditions include giant cell arteritis and Takayasu arteritis, with isolated aortitis being increasingly recognised in the literature and studied within this disease spectrum. Epidemiological studies have evidenced a worldwide distribution of Takayasu arteritis. In giant cell arteritis, distinct clinical phenotypes with specific outcomes (ie, cranial and large vessel forms) have been recognised. The advancements that have been made in vascular imaging have enabled improvement in diagnosis and classification of these diseases, although their value in follow-up continues to be assessed. Targeted therapies that can induce clinical remission with reduced glucocorticoid exposure are emerging. However, many patients develop vascular damage over time, highlighting the need for further understanding of the pathophysiological link between inflammation, vascular injury, and remodelling.

Introduction

Primary systemic vasculitis are a heterogeneous group of diseases involving immune-mediated inflammation of blood vessels in the absence of a known underlying disease, either autoimmune, infectious, or neoplastic.[1] In the most recent 2012 International Chapel Hill Consensus Conference (CHCC) nomenclature system, these diseases were divided according to the size of the vessels predominantly affected, with large-vessel vasculitis corresponding to those affecting the aorta, its major branches, or both.[1] Large-vessel vasculitis prototypes are giant cell arteritis and Takayasu arteritis, which despite sharing several common features, constitute distinct diseases with different epidemiology, pathophysiology, and clinical manifestations. The 2012 CHCC nomenclature recognised isolated aortitis for the first time, classifying it then as a single-organ vasculitis. However, unlike other conditions in this group (eg, primary CNS vasculitis and cutaneous vasculitis), isolated aortitis does not affect an organ per se, but rather the vascular territory that defines large-vessel vasculitis. Epidemiological, transcriptomic, and clinical evidence has suggested that isolated aortitis could be a limited expression of giant cell arteritis, which also conflicts with the definition of single-organ vasculitis proposed by the CHCC.

Other primary systemic vasculitic diseases as well as several other conditions, such as infections and systemic immune-mediated diseases, can also present with aortitis, although far less commonly than in giant cell arteritis, Takayasu arteritis, and isolated aortitis. These diseases are summarised along with their clinical features in table 1. This Seminar aims to comprehensively review giant cell arteritis, Takayasu arteritis, and isolated aortitis, with a focus on recent advances and open issues in epidemiology, clinical features, investigations, diagnosis, pathophysiological insights, and therapeutic approaches.

Epidemiology

Historically, epidemiological data have been reported as cases per 100 000 individuals aged 50 years or older for giant cell arteritis and as cases per 1 000 000 individuals for Takayasu arteritis. Giant cell arteritis is the most commonly reported form of primary systemic vasculitis, and is most often observed in populations with northern European ancestry.[2] The pooled incidence of giant cell arteritis was estimated to be 10·0 cases per 100 000 individuals aged 50 years or older per year in a meta-analysis, which highlighted the north–south gradient for its occurrence in Europe.[3] The highest incidence (in cases per 100 000 individuals aged 50 years or older per year) was found in Scandinavia (21·6), followed by North America and South America (10·8), Oceania (7·8), Europe (7·3), Middle East (5·73), Africa (4·62), and east Asia (0·34). Similar incidence rates have been reported in both White and Black patients.[4] The effect of age on the occurrence of giant cell arteritis was well evidenced in a biopsy-proven population of Swedish patients, with increasingly higher incidence rates (in cases per 100 000 individuals aged 50 years or older per year) for the age groups of individuals aged 50–60 years (2·0), 61–70 years (11·8), and 71–80 years (31·3).[5] The pooled prevalence of giant cell arteritis was calculated to be 51·7 cases per 100 000 individuals aged 50 years or older per year.[3]

Takayasu arteritis has been increasingly reported worldwide, with some regions showing higher prevalence rates over time, which suggests greater recognition, inclusion of patients from different ethnic backgrounds, or both. In a meta-analysis, the incidence of Takayasu arteritis was estimated to range between 0·70 and 1·76 per 1 000 000 individuals per year,[2,6] but there is considerable geographical variation in its occurrence. The highest prevalence rates (in cases per 1 000 000 individuals) are seen in Asia; specifically, Japan (40·0),[7] followed by South Korea (28·2)[8] and Türkiye (12·8 to 33·0),[9,10] contrasting with rates in China (11·7).[11] The range of prevalence rates in Europe (4·6–14·5)[2,12] is generally lower than those of Asia, but is higher than those observed in the USA (0·9–8·4) or Australia (3·9).[12–14] The influence of ethnicity on the occurrence of Takayasu arteritis is exemplified by two large population-based studies. In the

Sorbonne Universités, AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Département de Médecine Interne et Immunologie Clinique, F-75013, Paris, France (Prof P Cacoub MD MSc, M Vieira MD MSc, Prof D Saadoun MD PhD); **Centre National de Référence Maladies Autoimmunes Systémiques Rares, Centre National de Référence Maladies Autoinflammatoires et Amylose Inflammatoire (CEREMAIA), Paris, France** (Prof P Cacoub, M Vieira, Prof D Saadoun); **Inflammation–Immunopathology–Biotherapy Department (DMU 3iD); CIC Biotherapy, INSERM 959, Groupe Hospitalier Pitié-Salpêtrière, AP-HP, Paris, France** (Prof P Cacoub, M Vieira, Prof D Saadoun); **Department of Internal Medicine, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil** (M Vieira); **Department of Rheumatic and Immunologic Diseases, Cleveland Clinic, Cleveland, OH, USA** (Prof C A Langford MD MHS); **Department of Internal Medicine/Clinical Haematology, Ibn Sina University Hospital, Rabat, Morocco** (Prof Z Tazi Mezalek)

Correspondence to:
Prof Patrice Cacoub, Sorbonne Universités, AP-HP, Groupe Hospitalier Pitié-Salpêtrière, Département de Médecine Interne et Immunologie Clinique, F-75013, Paris 75013, France
patrice.cacoub@gmail.com
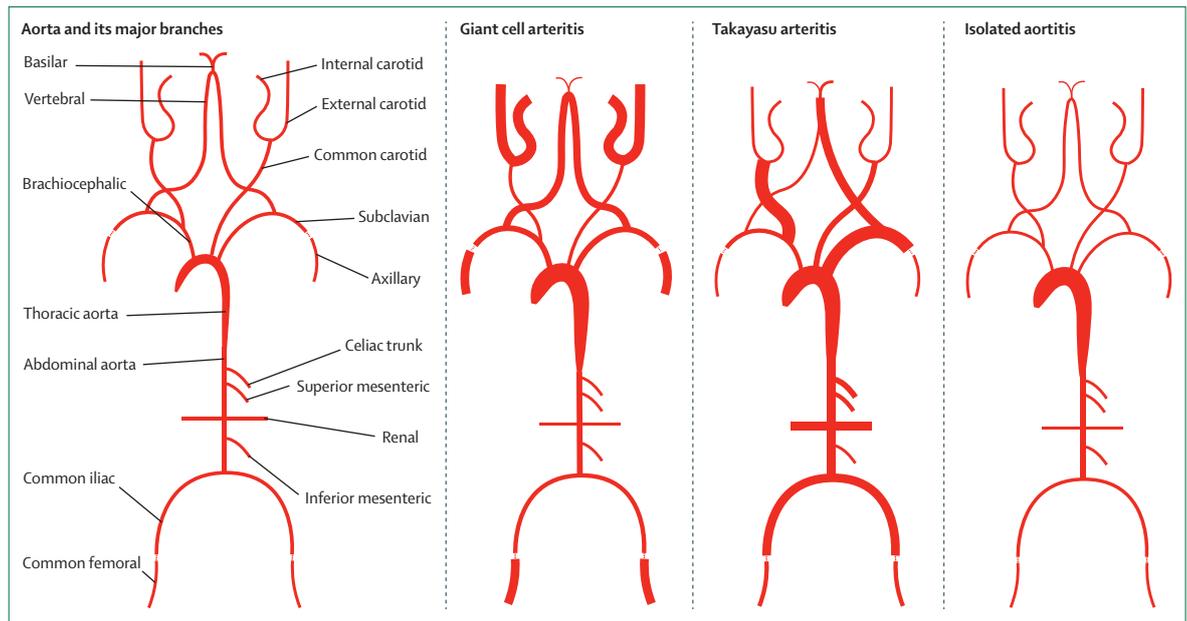
Figure 1: The aorta, its main branches, and how these are affected in giant cell arteritis, Takayasu arteritis, and isolated aortitis

Giant cell arteritis has a predilection for the thoracic aorta, internal and external carotid and its branches, vertebral, subclavian, and axillary arteries, although it can also particularly affect the iliac–femoral arteries, all in a generally symmetrical manner. In Takayasu arteritis, the entire length of the aorta can be affected, and supra-aortic branches (ie, subclavian, common carotid, and vertebral) are typically affected asymmetrically at first. Isolated aortitis is mostly restricted to the thoracic aorta, particularly its ascending portion.

first study, from southeastern Norway, the overall prevalence of 22·0 cases per 1 000 000 individuals was higher than the European average, with even higher rates seen in the few included patients with Asian or sub-Saharan African heritage.[15] In the second study, from Rio de Janeiro, Brazil, prevalence rates were found to be 16·9 cases per 1 000 000 individuals overall, and 25·1 in Black Brazilians.[16]

Only one small population-based epidemiological study on isolated aortitis has been carried out, showing an annual incidence of pathologically confirmed isolated aortitis of 8·9 per 1 000 000 individuals aged 50 years or older.[17] In a retrospective multicentre study of 5666 patients who had thoracic aortic surgery between 1997 and 2022, isolated aortitis accounted for 2·1% of aortic surgeries.[18]

Clinical presentation

The clinical presentations of giant cell arteritis, Takayasu arteritis, and isolated aortitis can be highly variable. Table 2 displays the distinctive vascular and extra-vascular features of these disease entities.

The increasing recognition of large-vessel involvement in giant cell arteritis has split it into two major phenotypes: a cranial phenotype, dominated by manifestations due to the involvement of the branches of the external and internal carotid arteries, and a large-vessel phenotype, dominated by inflammation of the aorta and its major branches. Patients with large vessel giant cell arteritis have a higher female predominance and a younger age of disease onset compared with individuals with cranial giant cell arteritis.[19] Cranial and large-vessel features often coexist;[20] this means that the potential for large-vessel involvement must be assessed in those presenting with cranial giant cell arteritis; and the risk of cranial features, including blindness, must always be considered as a possibility in those with large vessel giant cell arteritis.

In Takayasu arteritis, disease categorisation has focused on the distinction between childhood-onset and adult-onset, with earlier onset (ie, younger than 16 years or 18 years) being associated with a lower female predominance, more frequent cardiac and renal involvement, and higher mortality.[21–23] Another form of Takayasu arteritis categorisation concerns the angiographic types as proposed by Hata and colleages (graded type I to type V according to the affected arterial sites).[24] Patients with a more extensive disease— eg, type V, which involves the thoracic and abdominal aorta in addition to their branches—have increased morbidity.[25,26]

Regarding isolated aortitis, clinical presentation is most often asymptomatic and the diagnosis is usually made on the basis of histological analysis from aortic surgery or as a radiological finding of aortitis.

Vascular features

Aortic inflammation might present with non-specific symptoms, such as chest, back, lumbar, or abdominal pain, or even more vague symptoms, such as dry cough or dysphagia. Such symptoms can be present in giant cell

arteritis, Takayasu arteritis, and isolated aortitis. Ischaemic symptoms of the aortic arch branches (ie, brachiocephalic trunk, carotid, subclavian, and vertebral arteries) include syncope, subclavian steal syndrome, Raynaud's phenomenon, carotidynia, headaches, seizures, and visual disturbances. Involvement of the vessels supplying the upper and lower extremities can lead to claudication, vascular bruits, reduction or loss of pulses, and asymmetric blood pressures. How giant cell arteritis, Takayasu arteritis, and isolated aortitis affect the aorta and its main branches are presented in figure 1.

In giant cell arteritis, the involvement of the external carotid artery branches can produce temporal or occipital pulsatile headache, scalp tenderness, temporal artery abnormalities, and jaw or tongue claudication. Internal carotid artery involvement can manifest as amaurosis fugax, diplopia, and permanent blindness.[27] Most of the visual manifestations of giant cell arteritis are due to the involvement of the posterior ciliary arteries, resulting in an arteritic anterior ischaemic optic neuropathy or central artery occlusion, both of which might lead to irreversible visual loss. Historical cohorts documented visual loss in giant cell arteritis in 17 (37%) of 46 patients between 2009 and 2011, which might occur without preceding features.[28] These rates have decreased to less than 10% between 2012 and 2013 due to increased disease recognition and the introduction of giant cell arteritis fast-track clinics in specific geographical locations.[28] Stroke and transient ischaemic attack might occur, usually in the posterior fossa as the vertebral arteries are specifically affected in giant cell arteritis.[19] Axillary involvement is a characteristic feature of giant cell arteritis, occurring in around half of patients.[19] The iliac and femoral arteries might also be affected.

In Takayasu arteritis, the aorta is the most affected site, with around 80% of patients presenting with aortic involvement, followed by subclavian artery stenosis that affects around 70% of patients.[19] Involvement of the common carotid artery can lead to carotidynia or ischaemia in the anterior and middle cerebral territory. Ischaemic stroke and transient ischaemic attack are estimated to occur in up to 20% of patients with Takayasu arteritis.[29,30] Chronic ischaemia of the carotid territory can lead to central retinal hypoperfusion in up to 14% of patients with Takayasu arteritis.[31] Ischaemia in the vertebrobasilar territory might also occur (13% vs 87% in carotid territory), manifesting as seizures and dizziness.[30] Takayasu arteritis might affect the pulmonary arteries, which can present with chest pain and shortness of breath, where it can mimic a pulmonary embolism. The involvement of the abdominal aorta and its branches occurs frequently, notably the renal arteries where stenosis can lead to renovascular hypertension in approximately half of patients with Takayasu arteritis.[29] In patients with bilateral involvement of the subclavian arteries, blood pressure measurement might be compromised and the diagnosis of hypertension difficult.

	Disease features
Primary systemic vasculitis	
Giant cell arteritis	Temporal headache, amaurosis, jaw claudication, and polymyalgia rheumatica
Takayasu arteritis	Asymmetric blood pressure and peripheral pulses, extremity claudication, carotidynia, renal hypertension, and stroke
Isolated aortitis	Absence of extra-vascular features
Behçet's syndrome	Recurrent oral and genital ulcers, inflammatory skin lesions, uveitis, and deep vein thrombosis
Anti-neutrophil cytoplasmic autoantibody-associated vasculitis	Skin purpura, recurrent rhinosinusitis, pulmonary nodules, glomerulonephritis, and mononeuritis multiplex
Cogan's syndrome	Ocular inflammatory lesions (eg, keratitis, uveitis, episcleritis) and inner-ear disease (eg, sensorineural hearing loss, vestibular dysfunction)
Infections	
Tuberculosis	Chronic or subacute cough, lymphadenopathy, fever, night sweats, weight loss with potential and heterogenous extra-pulmonary manifestations in a context of known or possible exposure to *Mycobacterium tuberculosis*
Late syphilis	Dilated ascending thoracic aorta with aortic valve regurgitation, potentially accompanied by cutaneous and neurological manifestations
Other infections	*Streptococcus* spp, *Staphylococcus* spp, *Samnonella* spp, *Campylobacter* spp, *Coxiella brunetti*, *Brucella* spp, *Tropheryma whipplei*
Systemic immune-mediated diseases	
IgG4-related disease*	Fibro-inflammatory involvement of CNS, salivary and lacrimal glands, lymph nodes, thyroid, retroperitoneum, and lungs
Relapsing polychondritis	Inflammation of cartilage, notably ear, nose, and tracheobronchial tree with extensive extra-cartilaginous features
VEXAS syndrome†	Late-adult onset of recurrent fever, myelodysplastic syndrome, and inflammation involving the skin, lung, and cartilage
Spondyloarthritis	Sacroiliitis, peripheral arthritis, enthesitis, dactylitis, and anterior uveitis
Sarcoidosis	Pulmonary infiltrates with mediastinal lymphadenopathies with varied extra-pulmonary manifestations
Rheumatoid arthritis	Polyarthritis with possible joint deformities, skin nodules, episcleritis, and other potential extra-articular features
Systemic lupus erythematous	Malar rash, photosensitivity, alopecia, polyarthritis, pleuro-pericarditis, glomerulonephritis, polyneuropathy, and other systemic manifestations
Other	
Erdheim-Chester*	Multifocal sclerotic lesions of the long bones, with potential infiltration of extra-osseous tissues (eg, heart, CNS, kidney, and skin)
Intravascular large B-cell lymphoma	Fever, night sweats, and weight loss without lymphadenopathy, but variably accompanied by CNS, skin, bone marrow, spleen, and liver involvement
Treatment-related	Related to use of immune checkpoint inhibitors (PD1 and CTLA-4 antagonists), filgastrim, and radiation therapy

VEXAS=Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic. *Aortic involvement in these conditions is usually described as a periaortitis, in which an inflammatory process arises from the aortic adventitia and extends into the surrounding periaortic tissues. †VEXAS syndrome is caused by a somatic missense mutation in *UBA1*, an X-linked gene, that causes late-adult onset autoinflammatory disease predominantly in males; the varied clinical phenotype might resemble that of distinct systemic primary vasculitis, including large-vessel vasculitis, but the systemic condition it is most closely associated with is relapsing polychondritis.

Table 1: **Main causes and disease features of large-vessel vasculitis**

Since isolated aortitis does not usually affect any branches of the aorta, the non-specific aortic symptoms discussed earlier might be the few clinical features observed in symptomatic patients.

	Giant cell arteritis	Takayasu arteritis	Isolated aortitis
Overall incidence	10·0 cases per 100 000 individuals (older than 50 years) per year	1·1 per 1 000 000 individuals per year	8·9 per 1 000 000 individuals (older than 50 years) per year
Age tropism	Older than 50 years	Younger than 60 years	Older than 50 years
Female-to-male ratio	2–3 to 1	5–12 to 1	3 to 1
Ethnicity	Nordic; White	Asian; Maghrebian; African-American; White	NA
Geographical region	Northern Europe; North America	East Asia; Middle East; north Africa; Latin America; southern Europe	NA
Aortitis frequency	~67%	~80%	100%
Stenosis	Mildly present	Strongly present	Absent
Aneurysm	Strongly present	Moderately present	Strongly present
Cervical and cranial arteries	Strongly present (external and internal carotid branches, vertebral)	Strongly present (common and internal carotid, vertebral)	Absent
Thoracic arteries	Strongly present (thoracic aorta, subclavian)	Strongly present (thoracic aorta, brachiocephalic trunk, subclavian, pulmonary)	Strongly present (ascending aorta, aorta arch, descending aorta)
Abdominal arteries	Mildly present (abdominal aorta)	Stongly present (abdominal aorta, renal, coeliac trunk, mesenteric)	Mildly present (abdominal aorta)
Extremity arteries	Moderately present (axillary, iliac, femoral)	Moderately present (brachial, iliac)	Absent
Extra-vascular features	Polymyalgia rheumatica, constitutional symptoms, and peripheral synovitis	Constitutional symptoms, episcleritis, erythema nodosum, pyoderma gangrenosum, sacroiliitis, arthritis, and colitis	Constitutional symptoms

Table 2: Distinctive features between three main causes of primary aortitis

Extra-vascular and associated features

Constitutional symptoms and signs, including fatigue, anorexia, weight loss, and low-grade fever, might accompany large-vessel inflammation. In giant cell arteritis, such symptoms can represent a clinical challenge, as a small subset of patients present exclusively with fever of unknown origin. About half of the patients with giant cell arteritis have symptoms of polymyalgia rheumatica, with pain and stiffness of the shoulder, hip girdle, or both, together with features of systemic inflammation. Early recognition of a possible overlap between giant cell arteritis and polymyalgia rheumatica should be sought out, especially as polymyalgia rheumatica is known to be a much more common disease than giant cell arteritis—ie, the overall incidence rate of polymyalgia rheumatica was 95·9 per 100 000 people aged 40 years or older in the period 1990–2016 in a UK study.[32] In Takayasu arteritis, constitutional symptoms are described in the early phases of the disease before the evidence of arterial occlusions, but such symptoms might be absent in up to 80% of patients. Various inflammatory diseases can be associated with, precede, or complicate Takayasu arteritis, with therapeutic considerations sometimes of their own, such as Crohn's disease or spondyloarthritis. In isolated aortitis, low-grade fever and weight loss might be present in a third of patients.[33] Systemic inflammation can also manifest in tissues other than the arteries (table 2), notably in giant cell arteritis and Takayasu arteritis.

Investigations

Laboratory

Giant cell arteritis, Takayasu arteritis, and isolated aortitis do not currently have specific biomarkers for either diagnosis or disease activity. C-reactive protein, erythrocyte sedimentation rate, and fibrinogen concentrations are often elevated, but in addition to being non-specific, concentrations in the normal range do not rule out the diagnosis.
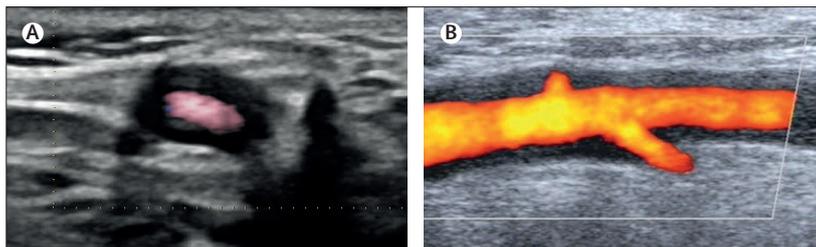
Imaging

Large-vessel imaging techniques are key tools both for the detection of structural lesions and possibly for vascular inflammation.[34] The available modalities include arterial ultrasound, CT angiography, magnetic resonance angiography, and [18F]fluorodeoxyglucose ([18F]FDG)-PET (usually combined with CT). PET-magnetic resonance is also a growing field and related to decreased radiation exposure. Given the availability and efficacy of these non-invasive techniques, catheter-directed dye arteriography is rarely used today, except for in specific interventions (eg, coronary arteriography). As morphological and metabolic vascular imaging studies have essentially focused on giant cell arteritis and Takayasu arteritis, the applications of the following modalities are generally extrapolated to isolated aortitis, except for ultrasound, due to its inability to assess the thoracic aorta.

Arterial ultrasound is often used early given its low cost, wide availability, and the absence of radiation exposure;

there is a high degree of inter-operator variability, and expertise in this setting is required. Bilateral ultrasound of temporal and axillary arteries is recommended as the first imaging modality for suspected giant cell arteritis with a pooled sensitivity estimated to be 88% and specificity to be 96%.[35] Acute arterial inflammation is typically represented by the non-compressible halo sign (figure 2), where there is homogeneous hypoechoic circumferential wall thickening that does not disappear with probe compression.[36] Although not pathognomonic, the presence of halo sign in both temporal and axillary arteries enhances the diagnostic performance of ultrasound in giant cell arteritis.[37] Arterial ultrasound can be useful in Takayasu arteritis, particularly in detecting structural lesions. Most arteries, except the descending thoracic aorta (eg, carotid, vertebral, subclavian, mesenteric, and renal arteries), can be accessed with ultrasound, although resolution decreases with deeper arteries.

Structural changes in the aorta can be assessed using either CT angiography (figure 3) or magnetic resonance angiography. Aortitis is defined by a circumferential wall thickening (>2·2 mm) on CT angiography.[38] Wall thickening can also be observed in the proximal large vessel branches, such as the axillary, renal, mesenteric, and iliac arteries. The advantages of magnetic resonance angiography (over CT angiography) are the absence of radiation, which is particularly important for young patients with Takayasu arteritis who will need numerous evaluations during their disease course, and the ability to assess arterial inflammation through contrast enhancement.[34,39] In addition to the aorta, high-resolution magnetic resonance angiography has been investigated in the examination of cranial vessels and orbital structures in giant cell arteritis, with good pooled sensitivity (81%) and high specificity (98%).[35] In patients with newly diagnosed giant cell arteritis, even those presenting with cranial giant cell arteritis, non-invasive imaging of the neck, chest, abdomen, or pelvic vessels with CT angiography or magnetic resonance angiography is advised to detect and determine the baseline extent of large-vessel involvement.

[18F]FDG-PET provides metabolic information (figure 4), with aortitis defined as grade III FDG uptake of the vascular wall, with a sensitivity of 85% and specificity of 83% in differentiating vasculitis from other conditions.[40] The absence of [18F]FDG-PET vascular uptake has been found to have a negative predictive value for angiographic lesion progression in both giant cell arteritis and Takayasu arteritis.[41] A more widespread vascular hypermetabolism at diagnosis (ie, a higher total vascular score) correlated with increased diameters in the thoracic aorta over the course of the disease.[42] As vascular uptake might persist due to vascular remodelling rather than inflammation, new markers other than labelled glucose have been tested, specifically targeting activated infiltrating macrophages or tissue-resident fibroblasts.[43,44]

Figure 2: Arterial inflammation in giant cell arteritis visualised by ultrasound
Arterial ultrasound is a low-cost and widely available technique, currently recommended as the first imaging modality for suspected giant cell arteritis. This technique is useful in detecting both structural lesions and inflammatory mural changes, such as the non-compressible halo sign shown in the temporal artery (A) and the axillary artery (B). The halo sign consists of a homogeneous, hypoechoic circumferential wall thickening that does not disappear with probe compression and is associated with good diagnostic accuracy, although not pathognomonic.

Histopathology

The temporal artery is the most common site from which vascular tissue is obtained for diagnostic purposes in giant cell arteritis; less frequently, the aorta is also available when a surgical treatment is required in giant cell arteritis, Takayasu arteritis, or isolated aortitis. All three diseases present with granulomatous vasculitis with transmural inflammatory infiltrates composed mainly of lymphocytes in the adventitia and macrophages in the media, which fuse to form giant cells within granulomas. The external and internal elastic laminae separating vascular layers are typically disrupted and necrosis of the media can also be present (figure 5).[1] Giant cell arteritis aortitis has prominent intimal thickening, whereas in Takayasu arteritis, the adventitia greatly expands with marked fibrosis. In both cases, the media is damaged, with the inner half (in contact with the intima) being more affected in giant cell arteritis, and the outer half (in contact with the adventitia) preferentially affected in Takayasu arteritis. The cellular composition of the immune infiltrates also differs, with CD4+ T lymphocytes and myeloid cells dominating in giant cell arteritis, whereas CD8+ T cells and B cells are also present in Takayasu arteritis.[45] Comparative studies of this nature for isolated aortitis are scarce. Despite these differences, the aortitis of giant cell arteritis, Takayasu arteritis, and isolated aortitis has a similar overall appearance. Within the four existing histopathological patterns—granulomatous or giant cell pattern, lymphoplasmacytic pattern, mixed inflammatory pattern, and the suppurative pattern[46]—the granulomatous or giant cell pattern is the most typical, although up to a third of cases might present the lymphoplasmacytic pattern.[18,46,47]

Diagnosis and classification

The diagnoses of giant cell arteritis, Takayasu arteritis, and isolated aortitis are made by collating the collective evidence obtained during the clinical and other investigative assessments while ruling out other possible causes (table 1). The increasing use of fast-track giant cell

Figure 3: Aortic structural changes in large-vessel vasculitis
CT angiography images are shown for patients with large-vessel vasculitis. (A) Aneurysm of the descending thoracic aorta with aortic wall thickening (arrow) in a patient with giant cell arteritis. (B) Arterial wall thickening of the branches of the aortic arch, particularly at the origin of the brachiocephalic trunk, the left common carotid artery, and the right subclavian (arrows) in a patient with Takayasu arteritis. (C) 3D reconstruction of the abdominal aorta showing ostial stenosis of both renal arteries (arrows) in a patient with Takayasu arteritis who previously had aortobifemoral bypass surgery.
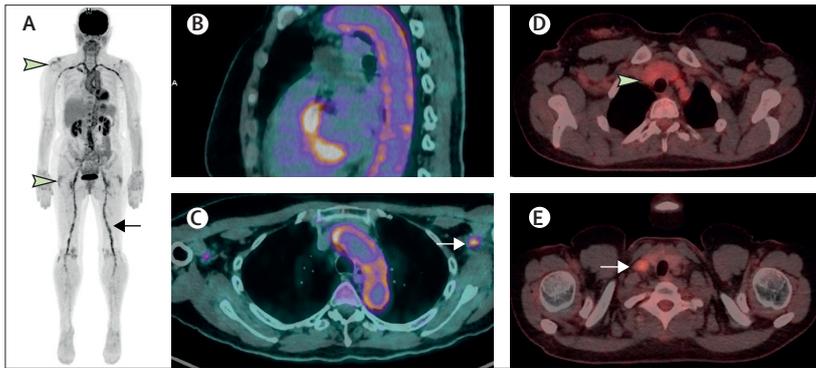
Figure 4: [¹⁸F]FDG-PET scan showing FDG uptake of the vascular wall
Arterial hypermetabolism on [¹⁸F]FDG-PET is defined as a grade III FDG uptake (higher than that of the liver), often presenting as a circumferential hypermetabolism. (A, B, and C) Intense hypermetabolism of thoracic aorta, subclavian, axillary (white arrow in C), common iliac and femoral arteries (black arrow in A) in a patient with active giant cell arteritis. Intense hypermetabolism is also noted in the shoulders' interspinous spaces as well as the peritrochanteric tuberosities (arrow heads in A) compatible with active polymyalgia rheumatica. (D and E) Moderate hypermetabolism at the origin of supra-aortic trunks (green arrow head in D), with asymmetrical hypermetabolism of right carotid artery (white arrow in E) in a patient with active Takayasu arteritis. FDG=fluorodeoxyglucose.

arteritis clinics reduces the delay between symptom onset and diagnosis, with a proven preventive effect on visual complications.[28] The diagnostic gold standard for giant cell arteritis has long been temporal artery biopsy, although comorbidities and age-related changes can make interpretation of such specimens difficult.[48] The sensitivity of temporal artery biopsy is decreased in patients with large vessel giant cell arteritis who present without cranial vessel involvement.[49,50] The diagnosis of giant cell arteritis should be ideally supported by either temporal artery ultrasound or biopsy. When there is a high clinical suspicion of giant cell arteritis along with a positive imaging result, a diagnosis can be made without further testing. Patients with low clinical probability (on the basis of all available clinical and laboratory data) and negative imaging can be considered unlikely to have giant cell arteritis. In the remaining scenarios, supplementary imaging, biopsy, or both, are strongly recommended.[34] For Takayasu arteritis, diagnostic criteria were proposed in 1996 by Sharma and colleagues, but have only been examined in relatively small Asian populations.[51] The diagnosis of isolated aortitis is often made as a histopathological discovery following surgery for an elective aortic aneurysm repair or urgent aortic dissection, or as a radiological finding in the absence of clinical features suggestive of systemic vasculitis.[18,47]

In terms of classification, robust criteria for giant cell arteritis and Takayasu arteritis have been jointly developed and validated by the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR; figure 6).[52,53] These criteria implement a cumulative scoring system and are intended for use within the context of research and not for the purpose of diagnosing individual patients. The limitations of previous classification criteria have been overcome, especially by incorporating non-invasive imaging techniques in the score and age-related entry criteria. The 2022 ACR–EULAR classification criteria for giant cell arteritis prespecifies an age of 50 years or older at diagnosis and has a sensitivity of 87·0% and specificity of 94·8%.[53] With late-onset Takayasu arteritis being increasingly recognised, the 2022 ACR–EULAR classification criteria for Takayasu arteritis include absolute entry criteria of an age of 60 years or younger at diagnosis and evidence of vasculitis on imaging. A patient can then be classified as Takayasu arteritis with a sensitivity of 93·8% and specificity of 99·2%.[52]

Diagnostic challenges can occur in atherosclerotic lesions in both patients with giant cell arteritis and older patients with Takayasu arteritis. Distinguishing between giant cell arteritis and Takayasu arteritis can also be challenging in patients with large-vessel disease occurring between the ages of 50 years and 60 years. There are currently no classification criteria for isolated aortitis.

Pathophysiology

Most of what is known about the mechanisms driving large-vessel inflammation comes from studies on giant cell arteritis and Takayasu arteritis that evaluate blood samples and temporal arteries (for giant cell arteritis), as

Figure 5: Histopathological frames from the three main causes of aortitis
(A) Lymphoid infiltrates (purple arrowhead) in the adventitia and giant cells agglomerates (green arrowhead) in the media of a patient with giant cell arteritis.
(B) Extensive and fibrous adventitial expansion, characteristic of Takayasu arteritis, in which there are some tertiary lymphoid structures (arrowheads). (C) A tertiary lymphoid structure in the adventitia (centre of the image) and hypertrophied vasa vasorum in the adventitia–media border in a patient with isolated aortitis (arrowhead; 10× high-power field).

Giant cell arteritis	Score
Absolute requirement	
Age ≥50 years at time of diagnosis	..
Additional clinical criteria	
Morning stiffness in shoulders or neck	+2
Sudden visual loss	+3
Jaw or tongue claudication	+2
New temporal headache	+2
Scalp tenderness	+2
Abnormal examination of the temporal artery (absent or diminished pulse, tenderness, or hard cord-like appearance)	+2
Laboratory, imaging, and biopsy criteria	
Maximum erythrocyte sedimentation rate ≥50 mm/h or maximum C-reactive protein concentration ≥10 mg/L before initiation of treatment for vasculitis	+3
Positive temporal artery biopsy or halo sign on temporal artery ultrasound	+5
Bilateral axillary involvement (ie, stenosis, occlusion, or aneurysm) on vascular imaging	+2
[18F]fluorodeoxyglucose-PET activity throughout aorta (uptake in the arterial wall greater than liver uptake through the descending thoracic and abdominal aorta)	+2

Takayasu arteritis	Score
Absolute requirement	
Age ≤60 years at time of diagnosis	..
Evidence of vasculitis on vascular imaging*	..
Additional clinical criteria	
Female sex	+1
Angina or ischaemic cardiac pain	+2
Arm or leg claudication	+2
Vascular bruit (ie, aorta, carotid, subclavian, axillary, brachial, renal, or iliofemoral arteries)	+2
Reduced pulse in upper extremity (ie, axillary, brachial, or radial arteries)	+2
Carotid artery abnormality (ie, reduction or absence of pulse of the carotid artery or tenderness of the carotid artery)	+2
Systolic blood pressure difference in arms ≥20 mm Hg	+1
Laboratory, imaging, and biopsy criteria	
One arterial territory†	+1
Two arterial territories†	+2
Three or more arterial territories†	+3
Symmetric involvement of paired arteries (carotid, subclavian, or renal arteries)	+1
Abdominal aorta involvement (eg, stenosis, occlusion, aneurysm) with renal or mesenteric involvement	+3

Figure 6: 2022 American College of Rheumatology and European Alliance of Associations for Rheumatology classification criteria for large-vessel vasculitis
Weighted items are added to obtain a final score. A patient is classified to have giant cell arteritis if a score of at least 6 points is obtained with a sensitivity of 87·0% and specificity of 94·8%. A patient is classified to have Takayasu arteritis if a cumulative score of at least 5 is obtained with a sensitivity of 93·8% and specificity of 99·2%. *Evidence of vasculitis in the aorta or branch arteries must be confirmed by vascular imaging (eg, CT angiography, catheter-based, magnetic resonance angiography, ultrasound, PET). †Only one number of territories should be choosen (one, two, or three or more); these territories include thoracic aorta, abdominal aorta, mesenteric carotids, and subclavian and renal arteries presenting luminal damage (eg, stenosis, occlusion, or aneurysm) detected by vascular imaging.

aortic tissue is only rarely and cross-sectionally obtained from surgical interventions. Figure 7 illustrates the possible common pathophysiological model for aorta inflammation.

The paradigm for large-vessel vasculitis pathophysiology involves the breakdown of the immune privilege of the arterial wall with the entry of myeloid and lymphoid cells via the vasa vasorum that crosstalk with resident stromal cells. This influx is hypothesised to be triggered by one or more antigens (exogenous, endogenous, or both) presented by antigen-presenting cells. The presence of unique microbiomes in the blood, aortas, and temporal arteries of patients with giant cell arteritis, Takayasu arteritis, and isolated aortitis has supported the notion that pathogens could have a role in these mechanisms.[54–56] Monocytes migrate across the tissue and first differentiate into macrophages and then into giant cells, whereas lymphocytes might organise themselves into tertiary lymphoid structures within the adventitial layer (figure 5C).

The resulting transmural inflammation is accompanied by an intense neovascularisation process, which ensures access for the infiltrating cells throughout the layers.[45] The disruption of stromal cell metabolism and consequent extracellular matrix imbalance have been increasingly recognised, both as perpetuators of inflammation and as orchestrators of the arterial remodelling process that ultimately leads to vascular damage.[57–59]

The strongest genetic associations found for both giant cell arteritis and Takayasu arteritis concern the major histocompatibility complex region, highlighting the relevance of antigen presentation. Multi-ethnic genome-wide association studies have shown that different antigen-presenting cells might be involved in this process, with the most implicated human leukocyte antigen (HLA) alleles in giant cell arteritis being class II (eg, HLA-DRB1*04), whereas those in Takayasu arteritis are class I (eg, HLA-B*52).[60,61] Other gene associations outside the HLA region were related to adaptive and
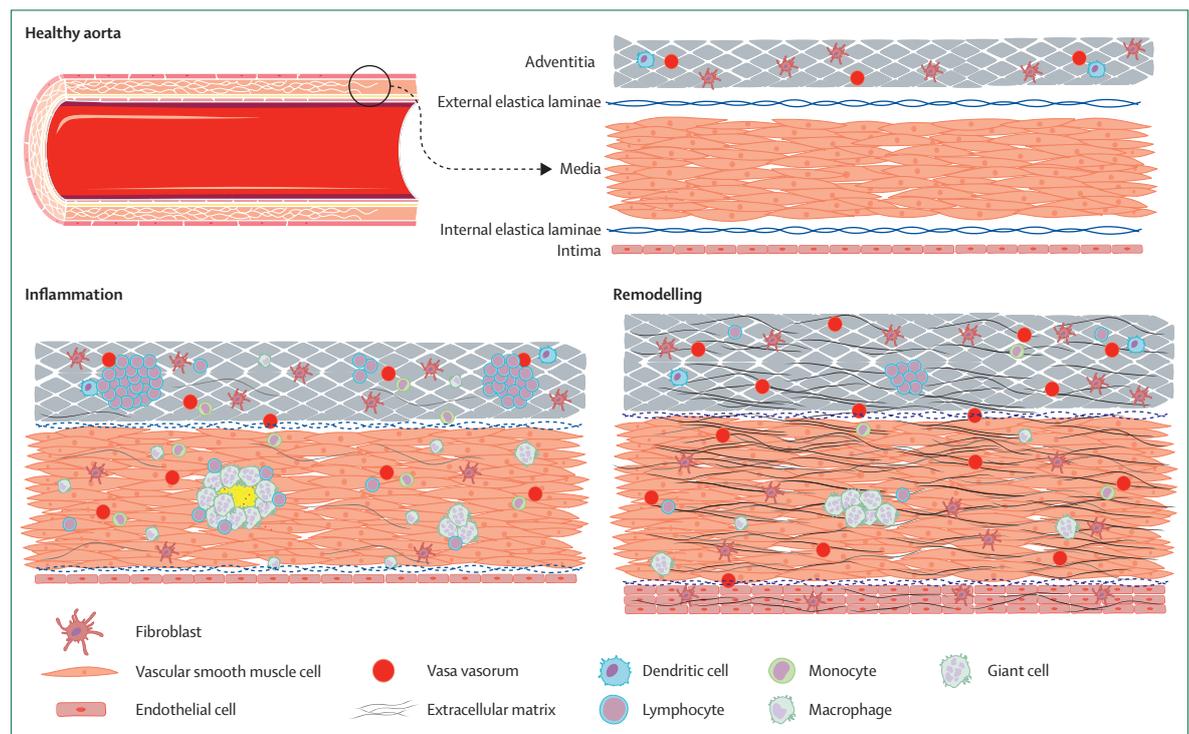
Figure 7: Possible common pathophysiological model for inflammation of the aorta
Large arteries are formed by three layers, divided by elastic lamina (external and internal). The outer layer, the adventitia, is composed mostly of fibroblasts and contains the vasa vasorum, which is the source of vascularisation for the whole arterial wall, as well as some sentinel dendritic cells that provide the aorta's immunoprivilege. The middle layer, the media, is composed almost exclusively of vascular smooth muscle cells, which are responsible for the tissue's contractility. The inner layer, the intima, is composed of a single layer of endothelial cells that coat the vessel's lumen. In large-vessel vasculitis, the recognition of an as yet unknown antigen triggers the influx of several immune cell subsets via the vasa vasorum in the adventitia. Lymphocytes can organise themselves into tertiary lymphoid structures and monocytes typically migrate across the tissue, first differentiating into macrophages and then into giant cells that will form granulomas. This transmural inflammation is accompanied by an intense neovascularisation throughout the layers, a disruption of external and then internal elastic lamina, and great disturbance in the extracellular matrix. The influx of cells and inflammatory reaction leads to a first enlargement of vessel wall thickness, where intima thickness might equal that of the media layer for example. Inflammation is mediated through the release of several cytokines (eg, TNF, IFNγ, IL-6, IL-17, etc), chemokines and growth factors (eg, GM-CSF), and matrix metalloproteinases by both immune and stromal cells. The exaggerated deposition of extracellular matrix and destruction of typical arterial wall architecture are thought to be mostly executed by fibroblasts and vascular smooth muscle cells, which might assume varied roles in situ. The interaction of tissue-resident stromal cells and tissue-infiltrating immune cells has a major role not only in triggering and perpetuating inflammation, but also orchestrating arterial remodelling. Both processes can therefore occur in parallel and to varying degrees. The exaggerated deposition of extracellular matrix might additionally contribute increased vessel wall thickness, this time specially in the adventitia layer.

innate immunity. Other genome-wide association studies have unravelled additional loci implicated in non-immune process, notably vascular remodelling and angiogenesis.[62,63]

In blood, the bridge between immune activation and stromal remodelling has been supported by recent plasma proteomic studies.[64,65] Circulating cells have shown plasticity towards inflammatory phenotypes, as exemplified in monocytes,[66,67] macrophages,[68,69] and lymphocytes. The polarisation of CD4+ T-helper cells typically elicits Th1 responses, responsible for INFγ and macrophage activation involved in vascular granulomatous inflammation. Th17 responses induce production of proinflammatory cytokines, such as IL-6 and TNF, which drive systemic inflammation.[70,71] These findings have a major effect on therapeutic approaches.

Within both the blood and arteries, T cells also differentiate into follicular T-helper cells,[72,73] which interact with B lymphocytes within tertiary lymphoid structures. These tertiary lymphoid structures might also contain CD4+ stem-like cells,[74] which are potentially autonomous in sustaining chronic inflammation at the tissue level. Vascular inflammation encompasses several pathways, some of which have therapeutic implications. The Janus kinase (JAK) signal transducer and activator of transcription (STAT) pathway is downstream to many proinflammatory cytokines in giant cell arteritis and Takayasu arteritis,[75,76] such as interferons and IL-6. Interferon signatures[77,78] and a senescence-associated secretory phenotype[79,80] have been described in the inflamed aortas of patients with both giant cell arteritis and Takayasu arteritis. Different immune checkpoints have also been reported to be disrupted within giant cell arteritis arteries.[81–83] In isolated aortitis, the very scarce data suggest that this entity is, from a transcriptomic point of view, closely related to giant cell arteritis.[78]

Most investigations have focused on pathways altered within infiltrating immune cells. Despite a growing literature on the potential role of resident stromal cells,[84–86] such as fibroblasts, vascular smooth muscle cells, and myofibroblasts, their phenotypic and functional characterisation is still poorly appreciated.

Management
Prognosis
Giant cell arteritis and Takayasu arteritis are chronic and relapsing conditions. Visual loss is often the most feared complication in patients presenting with cranial giant cell arteritis, typically occurring at diagnosis or shortly after treatment is initiated. Older age, jaw claudication, previous amaurosis fugax, and lower serum levels of inflammatory markers have been described as risk factors for its occurrence.[87] As for large vessel giant cell arteritis, the presence of aortic inflammation is associated with higher incidence of relapse, vascular complications, and death.[88–90] Relapses in either cranial or large vessel giant cell arteritis can consist of cranial or large-vessel features, polymyalgia rheumatica, and features of systemic inflammation, being further divided by some investigators into minor or major relapses. Major relapses are characterised either by clinical features of ischaemia (eg, jaw claudication, visual symptoms, stroke, and limb claudication) or active large-vessel inflammation resulting in dilatation, stenosis, or dissection, and account for about a quarter of all relapses.[91]

Over 40% of patients with Takayasu arteritis have a relapse after a median follow-up of 6 years.[29] Complications include new arterial occlusion or aneurysm and ischaemic cerebrovascular events. Progressive disease course, involvement of the thoracic aorta, and the presence of a retinopathy have been identified as risk factors for vascular complications.[92]

In patients who initially present with isolated aortitis, about 15% will exhibit systemic manifestations consistent with an alternative diagnosis over their follow-up, mostly of giant cell arteritis.[47] Patients who remain diagnosed with isolated aortitis have more vascular lesions and further surgical repair than patients with giant cell arteritis or Takayasu arteritis aortitis,[93,94] despite rarely exhibiting new clinical symptoms.[47]

Disease activity assessment
The assessment of disease activity is based on the interpretation of different clinical, laboratory, and radiological elements. Systemic and vascular symptoms are actively sought in an effort to define whether they reflect inflammatory activity or chronic previous damage, while eliminating alternative causes. As traditional inflammation biomarkers inconsistently reflect vascular inflammation, their typical values should not exclude disease activity, whereas elevated serum levels can occur in other settings, in particular infection. Radiological examinations are an important part of the assessment, as they can document new structural or functional alterations within the arterial wall. The frequency of obtaining follow-up imaging in the absence of new symptoms and signs in patients with Takayasu arteritis or known large-vessel involvement in giant cell arteritis varies between every 6 months and every 24 months, based on the recency of active disease and vessels being monitored. Specific activity scores combining these features exist for Takayasu arteritis,[95,96] but not for giant cell arteritis and isolated aortitis.

Strategies
The general objectives in the treatment of giant cell arteritis and Takayasu arteritis include an early resolution of clinical symptoms, normalisation of acute phase reactants, and vascular imaging stabilisation or improvement to avoid complications and relapses. Immunosuppressive medications are used to induce remission followed by remission maintenance. The optimal duration of treatment has not been specifically

addressed by studies and should be assessed on an individual basis depending on the development of relapses, vascular damage, and comorbidities. Patient-reported outcomes and quality of life should also be considered over the follow-up and have become important tools in clinical trials of these diseases.

In parallel, classic cardiovascular risk factors (eg, hypertension, diabetes, and smoking) should be assessed, as they might cause or aggravate arterial damage. A small evidence base has suggested potential benefits of aspirin,[97–99] β blockers,[100] and statins.[18] International guidelines[101–104] recommend considering antiplatelet therapy for giant cell arteritis and Takayasu arteritis in the case of vascular ischaemic complications, critical involvement of cervical or intracranial vessels, or high cardiovascular risk.

Vascular procedures might be required in the management of large vessel giant cell arteritis and Takayasu arteritis.[101,102] These procedures should be planned during the remission phase, as active disease is associated with an increased risk of complications.[105] The exception would be emergency situations, such as critical ischaemia or aneurysm dissection. In giant cell arteritis, Takayasu arteritis, and isolated aortitis, surgery can be indicated to address increasing size of an aortic aneurysm with a potential risk of rupture or dissection. In a large cohort of patients with giant cell arteritis-related aortitis, aneurysms tended to dissect at a smaller aortic diameter than atherosclerotic ones.[106] Although further validation is required, thresholds for surgical intervention might need to be lower in this setting. Other common elective indications in Takayasu arteritis include refractory hypertension (from renal artery stenosis or aorta coarctation), cerebral ischaemia (due to carotid and vertebral involvement), and stable stenosis causing disabling extremity claudication (eg, in subclavian, axillary, iliac, or femoral arteries), although the latter should generally be avoided given the potential for collateral circulation to develop. The choice of modality depends on multiple factors including the anatomical site being addressed, patient age, and comorbidities. Options include endovascular interventions or open surgery. Percutaneous procedures have been shown to be safe and effective in a large Indian cohort of patients with Takayasu arteritis (2450 arterial lesions in 942 patients) in addition to immunosuppressive treatment started before and continued in the long term,[107] although previous smaller series (166 procedures in 79 patients and 62 procedures in 20 patients) have suggested a higher rate of failure of percutaneous procedures compared with open surgery.[105,108]

Medications

Treatment regimens are generally based on a combination of glucocorticoids and synthetic or biological immunosuppressants (table 3). The initial regimen should be individualised and account for disease severity, vascular complications, comorbidities, and the supportive level of evidence for each drug. Given the long-term toxicity and frequent relapses that occur when glucocorticoids are used alone, the addition of another immunosuppressives is generally recommended as part of the initial treatment of both giant cell arteritis and Takayasu arteritis.[101,103,104] Glucocorticoid monotherapy, however, has been debated in patients with new-onset giant cell arteritis.[102] There is no current evidence that cranial giant cell arteritis should be treated differently to large vessel giant cell arteritis.[125] Given the scarcity of data on the management of isolated aortitis, the benefit of glucocorticoids or any other immunosuppressive treatments in isolated aortitis remains to be established.[93]

The mainstay of both giant cell arteritis and Takayasu arteritis treatment has been glucocorticoids.[101–104] Methylprednisolone pulses can be considered for severe, acute manifestations (eg, vision loss, amaurosis fugax, and acute cerebral ischaemia), although the supportive evidence is low. In giant cell arteritis, the initiation of glucocorticoids should not be delayed given the risk of permanent blindness. Classic regimens advocate a slow tapering of prednisone, aiming to reach 0–5 mg/day by 12 months for giant cell arteritis and 0–10 mg/day by 12 months for Takayasu arteritis.[102] The advent of biological therapies has investigated more rapid tapering regimens, with glucocorticoid discontinuation within 6 months.

Methotrexate is a synthetic immunosuppressive agent that has been used in combination with glucocorticoids. In giant cell arteritis, results with the use of methotrexate were mixed, with a single centre randomised clinical trial (n=42) showing a reduction in relapse and cumulative glucocorticoid dose,[126] whereas a larger multicentre randomised controlled trial (n=98) found that methotrexate had no effect on these parameters.[127] Together with a third randomised controlled trial (n=21),[128] their pooled data were meta-analysed, with methotrexate use being associated with a decreased risk of relapse and a reduction of cumulative glucocorticoid dose, although with no effect on reduction of glucocorticoid toxicity.[109] The place of methotrexate within the giant cell arteritis therapeutic strategy might be clarified by ongoing randomised controlled trials, such as a multicentre phase 3 in France (NCT03892785) and a phase 2 in Germany (NCT05623592). The strongest evidence for methotrexate in Takayasu arteritis comes from a small open-label study in which remission was achieved in 13 (81%) of 16 patients, allowing glucocorticoid tapering.[110] Retrospective and small open-label studies provide a rationale for the alternative use of other conventional immunosuppressives in Takayasu arteritis, such as leflunomide, mycophenolate mofetil, azathioprine, and cyclophosphamide.[102,104,114]

Tocilizumab is a monoclonal antibody against the IL-6 receptor, a key cytokine in large-vessel inflammation. The therapeutic benefit of tocilizumab in giant cell arteritis

	Dose and route of administration	Level of evidence in giant cell arteritis	Level of evidence in Takayasu arteritis	Major side-effects
Glucocorticoids	Oral: prednisone 0·5–1·0 mg/kg per day orally (initial dose), tapered to 0–10 mg over 6–12 months*; intravenous: methylprednisolone 250–1000 mg/day for 3 days, followed by oral prednisone regimens†	Randomised controlled trials (placebo arms); observational data	Observational data	Infections; hypertension; diabetes; Cushing's syndrome; osteoporosis; osteonecrosis; glaucoma; neuropsychiatric effects
Methotrexate	Oral or subcutaneous 15–25 mg weekly	Meta-analysis of placebo-controlled trials[109] (n=161, 7·5–15·0 mg/week, mean follow-up 54·7 weeks): prevention of first flare (HR=0·65, p=0·04; NNT 3·6) and second flare (HR=0·49, p=0·02; NNT 4·7) and sustained discontinuation of glucocorticoids for ≥24 weeks (HR=2·84, p=0·001)	Open-label trial[110] (n=16, mean follow-up 2·8 years): clinical and biological remission in 13 (81%) of 16 patients; observational data	Nausea and vomiting; diarrhoea; alopecia; hepatotoxicity; infections; cytopenia; pneumonitis
Tocilizumab‡ (anti-IL6)	Subcutaneous: 162 mg weekly; intravenous: 8 mg/kg monthly	Phase 3 double-blind placebo-controlled trial[111] (n=251) sustained remission at week 52: 56% tocilizumab plus 26-week prednisone taper, 18% placebo plus 52-week prednisone taper; phase 2 trial;[112] open-label prospective studies	Phase 3 double-blind placebo-controlled trial[113] (n=36): primary intention-to-treat time to relapse HR 0·41 (95% CI 0·15–1·10; p=0·059), per protocol analyses time to relapse HR 0·34 (0·11–1·00; p=0·034); meta-analyses[114,115] observational data	Injection site or infusion-related reactions; infections; gastrointestinal perforations; elevated transaminases; hyperlipidaemia; neutropenia; thrombocytopenia
TNF inhibitors	Intravenous: infliximab 5 mg/kg at week 0, 2, and 6, and then every 4–8 weeks; subcutaneous: adalimumab 40 mg every other week	Negative placebo-controlled trials[116–118]	Meta-analyses[115] (six observational controlled studies comparing TNF inhibitor to tocilizumab, n=491): similar rates of clinical remission (I^2=0%), angiographic stabilisation (I^2=52·5%), or adverse events (I^2=0%) compared with tocilizumab; observational data	Injection site or infusion-related reactions; neutropenia; infections; tuberculosis and other opportunistic infections; demyelinating disorders; heart failure; psoriasiform skin lesions; induction of autoantibodies and autoimmune reactions
JAK inhibitors‡	Oral: upadacitinib (JAK1 preferential inhibitor) 15 mg daily; tofacitinib (JAK1/3 inhibitor) 5 mg twice a day; baricitinib (JAK1/2 preferential inhibitor) 4 mg daily	Phase 3 double-blind placebo-controlled trial[119] (upadacitinib, n=428) sustained remission at week 52: upadacitinib plus 26-week prednisone taper 46%, placebo plus 52-week prednisone taper 29%; open-label prospective study[120] (baricitinib)	Open-label prospective studies[121,122] (tofacitinib vs methotrexate [n=53] or leflunomide [n=67]): complete response at 12 months=88·4% (vs 56·5% for methotrexate, p=0·02), effectiveness rate at 12 months=71·9% (vs 71·4% for leflunomide, p=1·00)	Infections; herpes zoster; venous and arterial thrombosis; malignancies; cytopenia; dyslipidaemia; gastrointestinal perforations
Secukinumab (anti-IL17)	Subcutaneous: 300 mg weekly for 4 weeks, and then every 4 weeks	Phase 2 double-blind placebo-controlled trial[123] (n=52) sustained remission at week 28: secukinumab plus 26-week prednisone taper 59%, placebo plus 26-week prednisone taper 8%	Open-label prospective study[124] (secukinumab vs TNF inhibitors, n=53): overall response at 6 months=52·6% (vs 64·7% for TNF inhibitors, p=0·38)	Injection site reactions; infections; fungal infections

HR=hazard ratio. NNT=number needed to treat. JAK=Janus kinase. *International recommendations on prednisone tapering regimens advocate a slow tapering, aiming to achieve 0–5 mg/day for giant cell arteritis and 0–10 mg/day for Takayasu arteritis by 12 months; randomised clinical trials in giant cell arteritis using tocilizumab, upadacitinib, and secukinumab have shown the value of using a 26-week prednisone taper. †Methylprednisolone pulses can be considered in case of severe and acute manifestations, such as vision loss (established or imminent) or acute organ ischaemia, with low supporting evidence for such. ‡Subcutaneous tocilizumab and intravenous tocilizumab (in some countries) and upadacitinib are the only label-approved treatments for large-vessel vasculitis so far, specifically for giant cell arteritis.

Table 3: Treatment options for giant cell arteritis and Takayasu arteritis

was proven in two independent placebo-controlled randomised controlled trials,[111,112] such that it has been proposed as part of the initial strategy.[101–103] In the largest of these randomised controlled trials, tocilizumab was able to induce sustained remission in 56 (56%) of 100 patients treated with weekly tocilizumab plus 26-week glucocorticoid taper, compared with 9 (18%) of 51 patients in the placebo group treated with a 52-week glucocorticoid taper.[111] The open-label extension of this study showed that for patients with giant cell arteritis who were in remission and discontinued tocilizumab, only 30–40% of patients maintained tocilizumab-free and glucocorticoid-free clinical remission over 2 years.[129] Prospective observational studies have assessed tocilizumab use in combination with shorter glucocorticoid regimens,[130–132] but such a strategy requires further validation (eg, in an upcoming prospective multicentre observational study in France NCT06271018). In Takayasu arteritis, tocilizumab was assessed against placebo in a small phase 3 randomised controlled trial that included refractory patients. Although this study failed to meet its primary intention-to-treat endpoint, per protocol analyses favoured tocilizumab over placebo in time to relapse.[113] In the 96-week open-label extension of this study, 24 (85%) of 28 patients who received tocilizumab were able to stabilise or improve their vascular imaging, and 13 (46%) were on low-dose prednisone.[133] Other prospective, retrospective, and

meta-analysis data support tocilizumab use in Takayasu arteritis, notably in severe or refractory settings.[115,134–136]

TNF inhibition in giant cell arteritis has been investigated in small randomised controlled trials where these were found to be ineffective.[116–118] TNF inhibitors have been used with success in patients with severe or refractory Takayasu arteritis, supported by open-label observational and meta-analysis data.[115,124,134,135] Abatacept (a CTLA-4 agonist) showed a potential reduction in the risk of giant cell arteritis relapses in a phase 2 randomised controlled trial,[137] which is being further explored through an ongoing phase 3 randomised controlled trial (NCT04474847). A phase 2 randomised controlled trial of abatacept in Takayasu arteritis showed no benefit in terms of relapse-free survival.[138]

Another interesting strategy focuses on inhibition of the JAK–STAT pathway. Favourable results were found in a small open-label proof-of-concept study of baricitinib in relapsing giant cell arteritis.[120] In a phase 3 randomised controlled trial (n=209), upadacitinib at a daily oral dose of 15 mg plus a 26-week glucocorticoid taper showed superiority over placebo plus a 52-week glucocorticoid taper in terms of sustained remission at week 52, with no major adverse cardiovascular events.[119] Given the warnings issued by regulatory agencies regarding the cardiovascular and cancer risks potentially associated with JAK inhibitor use,[139] their place in the management of giant cell arteritis is yet to be determined. Prospective studies have compared tofacitinib (a JAK1–3 inhibitor) to methotrexate or leflunomide in Takayasu arteritis where, despite considerable heterogeneity between groups, the results suggest that these treatments are roughly equivalent.[121,122]

Blocking IL-17 has been explored in giant cell arteritis, with a double-blind phase 2 randomised controlled trial[123] of secukinumab showing promising results, and a phase 3 multicentre study (NCT04930094) underway. In Takayasu arteritis, an observational study found secukinumab to be comparable to TNF inhibition in terms of complete response, relapse prevention, and glucocorticoid sparing at 6 months.[124]

Granulocyte-macrophage colony-stimulating factor is a multifunctional cytokine that has been shown to modulate Th1–Th17 responses in giant cell arteritis, in addition to a potential role in reducing arterial remodelling. The blockade of granulocyte-macrophage colony-stimulating factor with mavrilimumab was assessed in a double-blind phase 2 randomised controlled trial, where it proved superior to placebo in preventing giant cell arteritis relapses in patients previously in glucocorticoid-induced remission.[140]

Despite the effective blockade of several inflammatory pathways relevant to giant cell arteritis and Takayasu arteritis, the relatively low rates of sustained remission observed in randomised controlled trials of these modern treatments remain striking. Histological data from aortas and temporal arteries of patients in remission have revealed persistent vascular inflammation despite treatment, although the significance of this remains unclear.[141–143]

Conclusions and future perspectives

Giant cell arteritis, Takayasu arteritis, and isolated aortitis are diseases that evolve with large-vessel inflammation and, despite sharing many common aspects, constitute distinct entities. Their epidemiology, clinical spectrum, diagnostic methodology, and therapeutic strategies have seen substantial advances in the past decade. However, many knowledge gaps persist and provide opportunities for future advances. Epidemiological data have revealed the worldwide distribution of Takayasu arteritis, whereas the occurrence of isolated aortitis continues to be documented and explored. Giant cell arteritis has increasingly been recognised as having differing clinical phenotypes (ie, cranial and large vessel forms), whereas distinct patterns in Takayasu arteritis are still not well categorised. Imaging techniques have been increasingly incorporated into the diagnosis and follow-up of these patients, with new tracers holding promise. Randomised clinical trials of novel targeted strategies have provided new perspectives for more tailored treatment approaches that might reduce glucocorticoid exposure. Translational insights could contribute to the discovery of new circulating or radiological biomarkers for better diagnosing and monitoring these patients, as well as establishing the foundation for innovative therapeutic strategies targeting both inflammation and vascular remodelling. Progress in understanding these diseases is encouraging, with ongoing and future studies aiming at improving the management of these patients.

References
1 Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. *Arthritis Rheum* 2013; **65:** 1–11.
2 Watts RA, Hatemi G, Burns JC, Mohammad AJ. Global epidemiology of vasculitis. *Nat Rev Rheumatol* 2022; **18:** 22–34.
3 Li KJ, Semenov D, Turk M, Pope J. A meta-analysis of the epidemiology of giant cell arteritis across time and space. *Arthritis Res Ther* 2021; **23:** 82.
4 Gruener AM, Poostchi A, Carey AR, et al. Association of giant cell arteritis with race. *JAMA Ophthalmol* 2019; **137:** 1175–79.

5   Mohammad AJ, Nilsson JÅ, Jacobsson LTH, Merkel PA, Turesson C. Incidence and mortality rates of biopsy-proven giant cell arteritis in southern Sweden. *Ann Rheum Dis* 2015; **74:** 993–97.

6   Rutter M, Bowley J, Lanyon PC, Grainge MJ, Pearce FA. A systematic review and meta-analysis of the incidence rate of Takayasu arteritis. *Rheumatology* 2021; **60:** 4982–90.

7   Toshihiko N. Current status of large and small vessel vasculitis in Japan. *Int J Cardiol* 1996; **54** (suppl): S91–98.

8   Park SJ, Kim HJ, Park H, et al. Incidence, prevalence, mortality and causes of death in Takayasu arteritis in Korea—a nationwide, population-based study. *Int J Cardiol* 2017; **235:** 100–04.

9   Birlik M, Kücükyavas Y, Aksu K, et al. Epidemiology of Takayasu's arteritis in Turkey. *Clin Exp Rheumatol* 2016; **34** (suppl 97): S33–39.

10   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:** 911–16.

11   Sun Y, Kong X, Dai X, et al. Epidemiology of large vasculitis in Shanghai, China: a 10-year multicenter hospital-based study and systematic review. *Int J Rheum Dis* 2024; **27:** e15360.

12   Onen F, Akkoc N. Epidemiology of Takayasu arteritis. *Presse Med* 2017; **46:** e197–203.

13   Sanchez-Alvarez C, Crowson CS, Koster MJ, Warrington KJ. Prevalence of Takayasu arteritis: a population-based study. *J Rheumatol* 2021; **48:** 952.

14   Makin K, Isbel M, Nossent J. Frequency, presentation, and outcome of Takayasu arteritis in Western Australia. *Mod Rheumatol* 2017; **27:** 1019–23.

15   Gudbrandsson B, Molberg Ø, Garen T, Palm Ø. Prevalence, incidence, and disease characteristics of Takayasu arteritis by ethnic background: data from a large, population-based cohort resident in southern Norway. *Arthritis Care Res* 2017; **69:** 278–85.

16   Vieira M, Ochtrop MLG, Sztajnbok F, et al. The epidemiology of Takayasu arteritis in Rio de Janeiro, Brazil: a large population-based study. *J Clin Rheumatol* 2023; **29:** e100–03.

17   Kaymakci M, Elfishawi M, Langenfeld HE, et al. The epidemiology of pathologically confirmed clinically isolated aortitis: a north American population-based study. *Clin Exp Rheumatol* 2023; **41:** 956–60.

18   Espitia O, Bruneval P, Assaraf M, et al. Long-term outcome and prognosis of noninfectious thoracic aortitis. *J Am Coll Cardiol* 2023; **82:** 1053–64.

19   Saadoun D, Vautier M, Cacoub P. Medium- and large-vessel vasculitis. *Circulation* 2021; **143:** 267–82.

20   van der Geest KSM, Sandovici M, Bley TA, Stone JR, Slart RHJA, Brouwer E. Large vessel giant cell arteritis. *Lancet Rheumatol* 2024; **6:** e397–408.

21   Danda D, Goel R, Joseph G, et al. Clinical course of 602 patients with Takayasu's arteritis: comparison between Childhood-onset versus adult onset disease. *Rheumatology* 2021; **60:** 2246–55.

22   Kong F, Xu Y, Huang X, Lai J, Zhao Y. Childhood-onset versus adult-onset Takayasu arteritis: a study of 239 patients from China. *Joint Bone Spine* 2025; **92:** 105806.

23   Rathore U, Chandwar K, Singh K, Misra DP. Pediatric-onset Takayasu arteritis is associated with greater risk of mortality than adult-onset Takayasu arteritis—a systematic review with meta-analysis of observational cohort studies. *Semin Arthritis Rheum* 2024; **65:** 152355.

24   Hata A, Noda M, Moriwaki R, Numano F. Angiographic findings of Takayasu arteritis: new classification. *Int J Cardiol* 1996; **54** (suppl): S155–63.

25   Schmidt J, Kermani TA, Bacani AK, et al. Diagnostic features, treatment, and outcome of Takayasu arteritis in a US cohort of 126 patients. *Mayo Clin Proc* 2013; **88:** 822–30.

26   Hong S, Bae SH, Ahn SM, et al. Outcome of Takayasu arteritis with inactive disease at diagnosis: the extent of vascular involvement as a predictor of activation. *J Rheumatol* 2015; **42:** 489–94.

27   Vodopivec I, Rizzo JF 3rd. Ophthalmic manifestations of giant cell arteritis. *Rheumatology* 2018; **57** (suppl 2): ii63–72.

28   Patil P, Williams M, Maw WW, et al. Fast track pathway reduces sight loss in giant cell arteritis: results of a longitudinal observational cohort study. *Clin Exp Rheumatol* 2015; **33** (suppl 89): S-103–06.

29   Comarmond C, Biard L, Lambert M, et al. Long-term outcomes and prognostic factors of complications in Takayasu arteritis: a multicenter study of 318 patients. *Circulation* 2017; **136:** 1114–22.

30   Mirouse A, Deltour S, Leclercq D, et al. Cerebrovascular ischemic events in patients with Takayasu arteritis. *Stroke* 2022; **53:** 1550–57.

31   Elizalde J, Capella MJ. Takayasu's retinopathy. *Int Ophthalmol* 2011; **31:** 533–37.

32   Partington RJ, Muller S, Helliwell T, Mallen CD, Abdul Sultan A. Incidence, prevalence and treatment burden of polymyalgia rheumatica in the UK over two decades: a population-based study. *Ann Rheum Dis* 2018; **77:** 1750–56.

33   Espitia O, Samson M, Le Gallou T, et al. Comparison of idiopathic (isolated) aortitis and giant cell arteritis-related aortitis. A French retrospective multicenter study of 117 patients. *Autoimmun Rev* 2016; **15:** 571–76.

34   Dejaco C, Ramiro S, Bond M, et al. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice: 2023 update. *Ann Rheum Dis* 2024; **83:** 741–51.

35   Bosch P, Bond M, Dejaco C, et al. Imaging in diagnosis, monitoring and outcome prediction of large vessel vasculitis: a systematic literature review and meta-analysis informing the 2023 update of the EULAR recommendations. *RMD Open* 2023; **9:** e003379.

36   Chrysidis S, Duftner C, Dejaco C, et al. Definitions and reliability assessment of elementary ultrasound lesions in giant cell arteritis: a study from the OMERACT Large Vessel Vasculitis Ultrasound Working Group. *RMD Open* 2018; **4:** e000598.

37   Martins-Martinho J, Bandeira M, James L, Verdiyeva A, Fontes T, Rita Lopes A, et al. The value of axillary, facial, occipital, subclavian and common carotid arteries ultrasound in the diagnosis of giant cell arteritis. *Rheumatology* 2024; **64:** 1369–76.

38   Berthod PE, Aho-Glélé S, Ornetti P, et al. CT analysis of the aorta in giant-cell arteritis: a case–control study. *Eur Radiol* 2018; **28:** 3676–84.

39   Tso E, Flamm SD, White RD, Schvartzman PR, Mascha E, Hoffman GS. Takayasu arteritis: utility and limitations of magnetic resonance imaging in diagnosis and treatment. *Arthritis Rheum* 2002; **46:** 1634–42.

40   Grayson PC, Alehashemi S, Bagheri AA, et al. ^{18}F-fluorodeoxyglucose-positron emission tomography as an imaging biomarker in a prospective, longitudinal cohort of patients with large vessel vasculitis. *Arthritis Rheumatol* 2018; **70:** 439–49.

41   Quinn KA, Ahlman MA, Alessi HD, et al. Association of ^{18}F-fluorodeoxyglucose-positron emission tomography activity with angiographic progression of disease in large vessel vasculitis. *Arthritis Rheumatol* 2023; **75:** 98–107.

42   Moreel L, Coudyzer W, Boeckxstaens L, et al. Association between vascular ^{18}F-fluorodeoxyglucose uptake at diagnosis and change in aortic dimensions in giant cell arteritis: a cohort study. *Ann Intern Med* 2023; **176:** 1321–29.

43   Röhrich M, Rosales JJ, Hoppner J, et al. Fibroblast activation protein inhibitor-positron emission tomography in aortitis: fibroblast pathology in active inflammation and remission. *Rheumatology* 2024; **63:** 2473–83.

44   Ćorović A, Wall C, Nus M, et al. Somatostatin receptor PET/MR imaging of inflammation in patients with large vessel vasculitis and atherosclerosis. *J Am Coll Cardiol* 2023; **81:** 336–54.

45   Watanabe R, Berry GJ, Liang DH, Goronzy JJ, Weyand CM. Pathogenesis of giant cell arteritis and Takayasu arteritis— similarities and differences. *Curr Rheumatol Rep* 2020; **22:** 68.

46   Stone JR, Bruneval P, Angelini A, 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.

47   Clifford AH, Arafat A, Idrees JJ, et al. Outcomes among 196 patients with noninfectious proximal aortitis. *Arthritis Rheumatol* 2019; **71:** 2112–20.

48   Kendziora RW, Maleszewski JJ, Lin PT, et al. Age-related histopathological findings in temporal arteries. *Histopathology* 2023; **83:** 782–90.

49   Muratore F, Kermani TA, Crowson CS, et al. Large-vessel giant cell arteritis: a cohort study. *Rheumatology* 2015; **54:** 463–70.

50   de Boysson H, Daumas A, Vautier M, et al. Large-vessel involvement and aortic dilation in giant-cell arteritis. A multicenter study of 549 patients. *Autoimmun Rev* 2018; **17:** 391–98.

51   Sharma BK, Jain S, Suri S, Numano F. Diagnostic criteria for Takayasu arteritis. *Int J Cardiol* 1996; **54** (suppl): S141–47.

52 Grayson PC, Ponte C, Suppiah R, et al. 2022 American College of Rheumatology/EULAR classification criteria for Takayasu arteritis. *Ann Rheum Dis* 2022; **81:** 1654–60.

53 Ponte C, Grayson PC, Robson JC, et al. 2022 American College of Rheumatology/EULAR classification criteria for giant cell arteritis. *Ann Rheum Dis* 2022; **81:** 1647–53.

54 Getz TM, Hoffman GS, Padmanabhan R, et al. Microbiomes of inflammatory thoracic aortic aneurysms due to giant cell arteritis and clinically isolated aortitis differ from those of non-inflammatory aneurysms. *Pathog Immun* 2019; **4:** 105–23.

55 Hoffman GS, Getz TM, Padmanabhan R, et al. The microbiome of temporal arteries. *Pathog Immun* 2019; **4:** 21–38.

56 Desbois AC, Ciocan D, Saadoun D, Perlemuter G, Cacoub P. Specific microbiome profile in Takayasu's arteritis and giant cell arteritis. *Sci Rep* 2021; **11:** 5926.

57 Sutherland TE, Dyer DP, Allen JE. The extracellular matrix and the immune system: a mutually dependent relationship. *Science* 2023; **379:** eabp8964.

58 Xu S, Jiemy WF, Brouwer E, et al. Current evidence on the role of fibroblasts in large-vessel vasculitides: from pathogenesis to therapeutics. *Autoimmun Rev* 2024; **23:** 103574.

59 Karabayas M, Ibrahim HE, Roelofs AJ, Reynolds G, Kidder D, De Bari C. Vascular disease persistence in giant cell arteritis: are stromal cells neglected? *Ann Rheum Dis* 2024; **83:** 1100–09.

60 Carmona FD, Mackie SL, Martín JE, 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.

61 Ortiz-Fernández L, Saruhan-Direskeneli G, Alibaz-Oner F, et al. Identification of susceptibility loci for Takayasu arteritis through a large multi-ancestral genome-wide association study. *Am J Hum Genet* 2021; **108:** 84–99.

62 Carmona FD, Vaglio A, Mackie SL, et al. A genome-wide association study identifies risk alleles in plasminogen and P4HA2 associated with giant cell arteritis. *Am J Hum Genet* 2017; **100:** 64–74.

63 Borrego-Yaniz G, Ortiz-Fernández L, Madrid-Paredes A, et al. Risk loci involved in giant cell arteritis susceptibility: a genome-wide association study. *Lancet Rheumatol* 2024; **6:** e374–83.

64 Cunningham KY, Hur B, Gupta VK, et al. Plasma proteome profiling in giant cell arteritis. *Ann Rheum Dis* 2024; **83:** 1762–72.

65 Maughan RT, MacDonald-Dunlop E, Haroon-Rashid L, et al. Proteomic profiling of the large-vessel vasculitis spectrum identifies shared signatures of innate immune activation and stromal remodelling. *Arthritis Rheumatol* 2025; **77:** 884–900.

66 Estupiñán-Moreno E, Ortiz-Fernández L, Li T, et al. Methylome and transcriptome profiling of giant cell arteritis monocytes reveals novel pathways involved in disease pathogenesis and molecular response to glucocorticoids. *Ann Rheum Dis* 2022; **81:** 1290–300.

67 de Aguiar MF, Torquato H, Salu BR, et al. Monocyte subsets and monocyte-related chemokines in Takayasu arteritis. *Sci Rep* 2023; **13:** 2092.

68 Stankey CT, Bourges C, Haag LM, et al. A disease-associated gene desert directs macrophage inflammation through ETS2. *Nature* 2024; **630:** 447–56.

69 Veroutis D, Argyropoulou OD, Goules AV, et al. Senescent cells in giant cell arteritis display an inflammatory phenotype participating in tissue injury via IL-6-dependent pathways. *Ann Rheum Dis* 2024; **83:** 342–50.

70 Deng J, Younge BR, Olshen RA, Goronzy JJ, Weyand CM. Th17 and Th1 T-cell responses in giant cell arteritis. *Circulation* 2010; **121:** 906–15.

71 Saadoun D, Garrido M, Comarmond C, et al. Th1 and Th17 cytokines drive inflammation in Takayasu arteritis. *Arthritis Rheumatol* 2015; **67:** 1353–60.

72 Desbois AC, Régnier P, Quiniou V, et al. Specific follicular helper T cell signature in Takayasu arteritis. *Arthritis Rheumatol* 2021; **73:** 1233–43.

73 Monjo I, Nieto-Carvalhal B, Uyaguari M, et al. Circulating PD-1hi CXCR5- and CXCR5+ CD4 T cells are elevated in patients with newly diagnosed giant cell arteritis and predict relapse. *Rheumatology* 2025; **64:** 3996–4004.

74 Sato Y, Jain A, Ohtsuki S, et al. Stem-like CD4+ T cells in perivascular tertiary lymphoid structures sustain autoimmune vasculitis. *Sci Transl Med* 2023; **15:** eadh0380.

75 Zhang H, Watanabe R, Berry GJ, Tian L, Goronzy JJ, Weyand CM. Inhibition of JAK-STAT signaling suppresses pathogenic immune responses in medium and large vessel vasculitis. *Circulation* 2018; **137:** 1934–48.

76 Régnier P, Le Joncour A, Maciejewski-Duval A, et al. Targeting JAK/STAT pathway in Takayasu's arteritis. *Ann Rheum Dis* 2020; **79:** 951–59.

77 Vieira M, Régnier P, Maciejewski-Duval A, et al. Interferon signature in giant cell arteritis aortitis. *J Autoimmun* 2022; **127:** 102796.

78 Hur B, Koster MJ, Jang JS, Weyand CM, Warrington KJ, Sung J. Global transcriptomic profiling identifies differential gene expression signatures between inflammatory and noninflammatory aortic aneurysms. *Arthritis Rheumatol* 2022; **74:** 1376–86.

79 Jiemy WF, van Sleen Y, Graver JC, et al. Indication of activated senescence pathways in the temporal arteries of patients with giant cell arteritis. *Arthritis Rheumatol* 2023; **75:** 1812–18.

80 Fang C, Du L, Gao S, et al. Association between premature vascular smooth muscle cells senescence and vascular inflammation in Takayasu's arteritis. *Ann Rheum Dis* 2024; **83:** 1522–35.

81 Zhang H, Watanabe R, Berry GJ, et al. Immunoinhibitory checkpoint deficiency in medium and large vessel vasculitis. *Proc Natl Acad Sci USA* 2017; **114:** E970–79.

82 Régnier P, Le Joncour A, Maciejewski-Duval A, et al. CTLA-4 pathway is instrumental in giant cell arteritis. *Circ Res* 2023; **133:** 298–312.

83 Ohtsuki S, Wang C, Watanabe R, et al. Deficiency of the CD155-CD96 immune checkpoint controls IL-9 production in giant cell arteritis. *Cell Rep Med* 2023; **4:** 101012.

84 Greigert H, Ramon A, Genet C, et al. Neointimal myofibroblasts contribute to maintaining Th1/Tc1 and Th17/Tc17 inflammation in giant cell arteritis. *J Autoimmun* 2024; **142:** 103151.

85 Xu S, Jiemy WF, Boots AMH, et al. Altered plasma levels and tissue expression of fibroblast activation protein alpha in giant cell arteritis. *Arthritis Care Res* 2024; **76:** 1322–32.

86 Watanabe N, Hara Y, Nishito Y, et al. Tissue degrading and remodelling molecules in giant cell arteritis. *Rheumatology* 2025; **64:** 3095–103.

87 Liozon E, Dalmay F, Lalloue F, et al. Risk factors for permanent visual loss in biopsy-proven giant cell arteritis: a study of 339 patients. *J Rheumatol* 2016; **43:** 1393–99.

88 Kermani TA, Warrington KJ, Crowson CS, et al. Large-vessel involvement in giant cell arteritis: a population-based cohort study of the incidence-trends and prognosis. *Ann Rheum Dis* 2013; **72:** 1989–94.

89 Vautier M, Dupont A, de Boysson H, et al. Prognosis of large vessel involvement in large vessel vasculitis. *J Autoimmun* 2020; **108:** 102419.

90 Quick V, Abusalameh M, Ahmed S, et al. Relapse after cessation of weekly tocilizumab for giant cell arteritis: a multicentre service evaluation in England. *Rheumatology* 2023; **63:** 3407–14.

91 Narváez J, Domínguez-Álvaro M, Hernández-Rodríguez I, et al. Epidemiology of major and minor relapses in giant cell arteritis according to EULAR definitions: insights from the ARTESER registry. *Rheumatology* 2025; published online May 9. https://doi.org/10·1093/rheumatology/keaf237.

92 Mirouse A, Biard L, Comarmond C, et al. Overall survival and mortality risk factors in Takayasu's arteritis: a multicenter study of 318 patients. *J Autoimmun* 2019; **96:** 35–39.

93 Ferfar Y, Morinet S, Espitia O, et al. Long-term outcome and prognosis factors of isolated aortitis. *Circulation* 2020; **142:** 92–94.

94 Ferfar Y, Morinet S, Espitia O, et al. Spectrum and outcome of noninfectious aortitis. *J Rheumatol* 2021; **48:** 1583–88.

95 Kerr GS, Hallahan CW, Giordano J, et al. Takayasu arteritis. *Ann Intern Med* 1994; **120:** 919–29.

96 Misra R, Danda D, Rajappa SM, et al. Development and initial validation of the Indian Takayasu Clinical Activity Score (ITAS2010). *Rheumatology* 2013; **52:** 1795–801.

97 Nesher G, Berkun Y, Mates M, Baras M, Rubinow A, Sonnenblick M. Low-dose aspirin and prevention of cranial ischemic complications in giant cell arteritis. *Arthritis Rheum* 2004; **50:** 1332–37.

98 Lee MS, Smith SD, Galor A, Hoffman GS. Antiplatelet and anticoagulant therapy in patients with giant cell arteritis. *Arthritis Rheum* 2006; **54:** 3306–09.

99 Martínez-Taboada VM, López-Hoyos M, Narvaez J, Muñoz-Cacho P. Effect of antiplatelet/anticoagulant therapy on severe ischemic complications in patients with giant cell arteritis: a cumulative meta-analysis. *Autoimmun Rev* 2014; **13:** 788–94.

100 Dumont A, Labombarda F, Gallou S, et al. Preventive effect of beta-blockers in the development of aortic dilation in giant cell arteritis-related aortitis. *Semin Arthritis Rheum* 2022; **57:** 152117.

101 Maz M, Chung SA, Abril A, et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the management of giant cell arteritis and Takayasu arteritis. *Arthritis Rheumatol* 2021; **73:** 1349–65.

102 Hellmich B, Agueda A, Monti S, et al. 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. *Ann Rheum Dis* 2020; **79:** 19–30.

103 Scolnik M, Brance ML, Fernández-Ávila DG, et al. Pan American League of Associations for Rheumatology guidelines for the treatment of giant cell arteritis. *Lancet Rheumatol* 2022; **4:** e864–72.

104 de Souza AWS, Sato EI, Brance ML, et al. Pan American League of Associations for Rheumatology guidelines for the treatment of Takayasu arteritis. *J Clin Rheumatol* 2023; **29:** 316–25.

105 Saadoun D, Lambert M, Mirault T, et al. Retrospective analysis of surgery versus endovascular intervention in Takayasu arteritis: a multicenter experience. *Circulation* 2012; **125:** 813–19.

106 Kebed DT, Bois JP, Connolly HM, et al. Spectrum of aortic disease in the giant cell arteritis population. *Am J Cardiol* 2018; **121:** 501–08.

107 Joseph G, Thomson VS, Attumalil TV, et al. Outcomes of percutaneous intervention in patients with Takayasu arteritis. *J Am Coll Cardiol* 2023; **81:** 49–64.

108 Liang P, Tan-Ong M, Hoffman GS. Takayasu's arteritis: vascular interventions and outcomes. *J Rheumatol* 2004; **31:** 102–06.

109 Mahr AD, Jover JA, Spiera RF, et al. Adjunctive methotrexate for treatment of giant cell arteritis: an individual patient data meta-analysis. *Arthritis Rheum* 2007; **56:** 2789–97.

110 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:** 578–82.

111 Stone JH, Tuckwell K, Dimonaco S, et al. Trial of tocilizumab in giant-cell arteritis. *N Engl J Med* 2017; **377:** 317–28.

112 Villiger PM, Adler S, Kuchen S, et al. Tocilizumab for induction and maintenance of remission in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial. *Lancet* 2016; **387:** 1921–27.

113 Nakaoka Y, Isobe M, Takei 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.

114 Misra DP, Rathore U, Patro P, Agarwal V, Sharma A. Disease-modifying anti-rheumatic drugs for the management of Takayasu arteritis—a systematic review and meta-analysis. *Clin Rheumatol* 2021; **40:** 4391–416.

115 Misra DP, Singh K, Rathore U, et al. The effectiveness of tocilizumab and its comparison with tumor necrosis factor alpha inhibitors for Takayasu arteritis: a systematic review and meta-analysis. *Autoimmun Rev* 2023; **22:** 103275.

116 Hoffman GS, Cid MC, Rendt-Zagar KE, et al. Infliximab for maintenance of glucocorticosteroid-induced remission of giant cell arteritis: a randomized trial. *Ann Intern Med* 2007; **146:** 621–30.

117 Seror R, Baron G, Hachulla E, 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.

118 Martínez-Taboada VM, Rodríguez-Valverde V, Carreño L, 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.

119 Blockmans D, Penn SK, Setty AR, et al. A phase 3 trial of upadacitinib for giant-cell arteritis. *N Engl J Med* 2025; **392:** 2013–24.

120 Koster MJ, Crowson CS, Giblon RE, et al. Baricitinib for relapsing giant cell arteritis: a prospective open-label 52-week pilot study. *Ann Rheum Dis* 2022; **81:** 861–67.

121 Kong X, Sun Y, Dai X, et al. Treatment efficacy and safety of tofacitinib versus methotrexate in Takayasu arteritis: a prospective observational study. *Ann Rheum Dis* 2022; **81:** 117–23.

122 Wang J, Dai X, Ma L, et al. Efficacy and safety of tofacitinib versus leflunomide with glucocorticoids treatment in Takayasu arteritis: a prospective study. *Semin Arthritis Rheum* 2022; **55:** 152018.

123 Venhoff N, Schmidt WA, Bergner R, et al. Safety and efficacy of secukinumab in patients with giant cell arteritis (TitAIN): a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Rheumatol* 2023; **5:** e341–50.

124 Tian X, Li M, Jiang N, et al. Comparative efficacy of secukinumab versus tumor necrosis factor inhibitors for the treatment of Takayasu arteritis. *Arthritis Rheumatol* 2023; **75:** 1415–23.

125 Blanco R, Aldasoro V, Maiz O, et al. Tocilizumab in cranial and extracranial giant cell arteritis: a national multicentre study of 471 cases. *Rheumatology* 2025; **64:** 2928–36.

126 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 Intern Med* 2001; **134:** 106–14.

127 Hoffman GS, Cid MC, Hellmann DB, et al. A multicenter, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis. *Arthritis Rheum* 2002; **46:** 1309–18.

128 Spiera RF, Mitnick HJ, Kupersmith M, 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.

129 Stone JH, Han J, Aringer M, et al. Long-term effect of tocilizumab in patients with giant cell arteritis: open-label extension phase of the Giant Cell Arteritis Actemra (GiACTA) trial. *Lancet Rheumatol* 2021; **3:** e328–36.

130 Christ L, Seitz L, Scholz G, et al. Tocilizumab monotherapy after ultra-short glucocorticoid administration in giant cell arteritis: a single-arm, open-label, proof-of-concept study. *Lancet Rheumatol* 2021; **3:** e619–26.

131 Muratore F, Marvisi C, Cassone G, et al. Treatment of giant cell arteritis with ultra-short glucocorticoids and tocilizumab: the role of imaging in a prospective observational study. *Rheumatology* 2024; **63:** 64–71.

132 Unizony S, Matza MA, Jarvie A, O'Dea D, Fernandes AD, Stone JH. Treatment for giant cell arteritis with 8 weeks of prednisone in combination with tocilizumab: a single-arm, open-label, proof-of-concept study. *Lancet Rheumatol* 2023; **5:** e736–42.

133 Nakaoka Y, Isobe M, Tanaka Y, et al. Long-term efficacy and safety of tocilizumab in refractory Takayasu arteritis: final results of the randomized controlled phase 3 TAKT study. *Rheumatology* 2020; **59:** 2427–34.

134 Alibaz-Oner F, Kaymaz-Tahra S, Bayındır Ö, et al. Biologic treatments in Takayasu's arteritis: a comparative study of tumor necrosis factor inhibitors and tocilizumab. *Semin Arthritis Rheum* 2021; **51:** 1224–29.

135 Mekinian A, Biard L, Dagna L, et al. Efficacy and safety of TNF-α antagonists and tocilizumab in Takayasu arteritis: multicentre retrospective study of 209 patients. *Rheumatology* 2022; **61:** 1376–84.

136 Wang J, Kong X, Ma L, et al. Treatment efficacy and safety of adalimumab versus tocilizumab in patients with active and severe Takayasu arteritis: an open-label study. *Rheumatology* 2023; **63:** 1359–67.

137 Langford CA, Cuthbertson D, Ytterberg SR, et al. A randomized, double-blind trial of abatacept (CTLA-4Ig) for the treatment of giant cell arteritis. *Arthritis Rheumatol* 2017; **69:** 837–45.

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

139 Ytterberg SR, Bhatt DL, Mikuls TR, et al. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. *N Engl J Med* 2022; **386:** 316–26.

140 Cid MC, Unizony SH, Blockmans D, et al. Efficacy and safety of mavrilimumab in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis* 2022; **81:** 653–61.

141 Maleszewski JJ, Younge BR, Fritzlen JT, 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.

142 Kaymakci MS, Boire NA, Bois MC, et al. Persistent aortic inflammation in patients with giant cell arteritis. *Autoimmun Rev* 2023; **22:** 103411.

143 Ricordi C, Marvisi C, Macchioni P, et al. Does tocilizumab eliminate inflammation in GCA? A cohort study on repeated temporal artery biopsies. *RMD Open* 2024; **10:** e005132.