Introduction

Large vessel vasculitis (LVV) is defined as inflammation affecting the aorta and its major branches [1]. Takayasu arteritis (TAK) and giant cell arteritis (GCA) comprise the two main variants of LVV. Historically, these two conditions have been considered separate entities because of the observed differences in the age of onset, presenting clinical features, geographic distribution and location of arterial involvement. However, some have proposed that TAK and GCA may exist within a clinical spectrum of a single disease [2-5]. Though this suggestion was originally raised over four decades ago [2], recent advances in non-invasive imaging have provided further evidence substantiating a potential phenotypic overlap. By definition, all patients with TAK demonstrate arterial narrowing or occlusion within the large arteries. Early systematic autopsy studies showed involvement of large vessels was also nearly ubiquitous in patients with GCA [6,7]. Nevertheless, to differentiate from other forms of vasculitis, initial descriptions of GCA focused predominantly on cranial features related to involvement of the temporal and ophthalmic arteries; vessels which are rarely compromised in TAK. With advances in imaging it is now better understood that a high proportion of patients with GCA also demonstrate extracranial large vessel involvement, similar to that seen in TAK. Indeed, prospective studies have shown that 67% of newly diagnosed GCA cases have large vessel involvement on computed...
tomography angiography [8] and up to 83% have evidence of vascular inflammation in the aorta and its major branches observed on positron emission tomography [9]. Differentiation between “classic” presentations of TAK and cranial GCA is rarely the focus of debate. However, controversy surrounds the attempt to classify patients with LVV aged 40–50 years of age as well as older individuals with LV in the absence of cranial manifestations. These patients often do not fulfill criteria for either condition. This article will focus on the current criteria for TAK and GCA and discusses both their usefulness and limitations in defining these conditions.

**Classification and diagnostic criteria**

The primary limitation in using criteria to assist in the separation of TAK from GCA is rooted in the frequent incorrect use of classification criteria as diagnostic criteria in routine daily practice. Understanding the definition and intent of each of these criteria types is therefore of utmost importance. To provide a diagnosis is to determine the cause of an illness based on the signs, symptoms and associated tests in a given individual patient. Diagnostic criteria, therefore, are a set of signs, symptoms and tests that can be used in routine clinical practice to determine the cause of an illness and guide the care of an individual patient. The aim of diagnostic criteria is to identify all patients with a disease, including those with unusual presentations.

Classification criteria, on the other hand, are standardized definitions developed with the intent of creating homogenous cohorts for research purposes, such that there is compatibility across studies. In order to achieve this homogenous population, the most common or well-defined phenotypes are chosen at the expense of atypical presentations. In addition, disease features are included based more on their specificity rather than sensitivity. If the sensitivity and specificity of classification criteria were both 100% they would be synonymous with and function as diagnostic criteria [11]. Nevertheless, this is not the case as classification criteria are imperfect and therefore will always result in a number of misclassified patients.

Due to the complexity and heterogeneity of rheumatic diseases, few validated diagnostic criteria exist in rheumatology. In addition, the performance of diagnostic criteria can be impacted dramatically by differences in disease epidemiology as well as the severity of disease manifestations in different practice settings. Because of this, the American College of Rheumatology (ACR) has taken a stance to only provide approval of classification criteria and will no longer endorse funding or approval of diagnostic criteria [10].

As such, to date there have been no approved or endorsed diagnostic criteria for GCA. Diagnostic criteria for TAK [12–14] have been proposed by centers in India and Japan (table I). However, these criteria have not been prospectively validated in other populations, limiting their utility. As a result, the diagnosis of GCA and TAK is based on patient demographic characteristics, clinical features, laboratory results, histopathology, and diagnostic imaging. Although not recommended, classification criteria are often employed in clinical practice for establishing a diagnosis, partly due to the lack of other objective tools such as specific biomarkers. Clinicians are often faced with patients demonstrating evidence of LV that meet both, or fail to meet either, of the current ACR 1990 classification criteria for TAK [15] or GCA [16] (table II). In a retrospective cohort study of patients with GCA, the majority (95%) of those with typical cranial manifestations met the ACR classification criteria for GCA. However, only about 40% of patients with large vessel GCA (LV-GCA; often also termed “extracranial” GCA) fulfilled the 1990 criteria, underscoring the inadequacy of the 1990 criteria [17]. A similar frustration is experienced by researchers trying to categorize patients for enrollment in clinical studies. This is evidenced, in part, by a recent survey of international vasculitis experts in which 38% and 45% of respondents expressed dissatisfaction with the current ACR classification criteria for TAK and GCA, respectively [18].

To date, the main areas of focus for both diagnostic and classification criteria of LVV include age of onset, inflammatory markers, vascular symptoms, angiographic arterial distribution and histopathology.

**Age**

Age at disease onset has been traditionally used as the primary clinical discriminator between TAK (< 40 years) and GCA (≥ 50 years). However, inadequacies with suggested age cutoffs have been present since the conception of this criterion. Ishikawa and colleagues evaluated 96 Japanese patients with TAK to develop an early set of proposed diagnostic criteria [12]. The average age at disease onset in this cohort was 32.1 ± 10.6 years (range 16 to 63 years). While age at onset < 40 years was suggested by this group to be an obligatory diagnostic criterion, 21 (22%) patients in this study were outside the proposed age cutoff. In development of the 1990 ACR TAK classification criteria, 63 patients with TAK were prospectively enrolled and compared to 744 control patients with other vasculitides. Though age at disease onset ≤ 40 years was decided on as one of the six criteria, 4 (6%) patients in this cohort were over 40 years old. In addition, while the age criterion had a relatively high sensitivity (95.2%), its specificity was the lowest among the six included criteria (68.1%) and had the 18th lowest specificity among the 22 potential variables evaluated [15]. Similar issues were encountered during the development of classification criteria for GCA in which the age criterion of ≥ 50 years had a high sensitivity (98.6%) but the second lowest specificity (63.8%) among the five proposed criteria and the 32nd lowest specificity among 33 variables considered [16].

Several authors consider age restriction to be arbitrary and without etiologic or pathophysiologic basis [4,13,19]. Indeed,

Sharma and colleagues [13] proposed modifications to the Ishikawa diagnostic criteria by removing the obligatory (age ≤ 40 years) criterion and also eliminating age restriction at diagnosis of hypertension. In doing so, sensitivity of diagnosing TAK increased from 84% to 96% while maintaining a specificity of 96%.

Despite its limitations, age demarcation has become time-honored and engrained in the vast majority of prospective and retrospective studies on LVV. Since definitions are not universally consistent, there is often a classification and/or selection bias in descriptive studies dependent upon how the researchers define TAK and GCA in their study population. The reason for such
variation in definitions occurs because current classification criteria do not address those with age of symptom onset between 40 and 50 years of age and provide limited utility for older patients with LVV in the absence of cranial features. Studies evaluating LVV have provided varying results regarding the importance of age in disease classification. In a retrospective observational study, Furuta et al. used latent class analysis to identify unobservable subgroups among 46 sequential patients with LVV [20]. No single item was specific for TAK or GCA in the latent class analysis, but there was grouping into two latent classes based on age < or ≥ 50 years in combination with other clinical and radiologic criteria. Because of the inherent use of age in the study enrollment criteria, repeat analysis without age as a sensitivity analysis was performed and showed similar results. These findings led the authors to suggest that an age cutoff of 50 years between the two conditions is legitimate [20].

Due to the difficulty in distinguishing between what could be considered either late-onset TAK or LV-GCA, future revisions of classification criteria will need to address modifying, or perhaps even removing, age cutoffs. While it is plausible that TAK and GCA are on a spectrum of the same disease with phenotypic variance determined by age-related immunologic and vascular alterations [4], such speculations have yet to be confirmed.

**Inflammatory markers**

A systemic inflammatory response is a common finding among vasculitides, particularly LVV. To date, investigations into disease specific biomarkers have unfortunately failed to identify auto-antibodies or other serologic molecules that would be useful in establishing the diagnosis or monitoring disease activity. As a result, non-specific acute phase reactants including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) have been relied upon both for diagnosis and management of GCA and TAK. While the majority of patients with newly diagnosed LVV will demonstrate an elevated ESR or CRP, this is not universal [21,22]. The 1990 ACR classification criteria highlighted early on a difference among ESR values between TAK and GCA, with GCA generally demonstrating a more robust inflammatory response. While ESR ≥ 50 mm/h has a good sensitivity (86.5%) and modest specificity (47.7%) for GCA [16], this parameter has both poor sensitivity (57.6%) and specificity (37.5%) for TAK [15].

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**TABLE II**

1990 American College of Rheumatology criteria for classification of large vessel vasculitis

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Age at disease onset &lt; 40 years: Development of symptoms or findings beginning younger than 40</td>
<td>Age at disease onset ≥ 50 years: development of symptoms or findings beginning at age 50 or older</td>
</tr>
<tr>
<td>Claudication of extremities: development and worsening of fatigue and discomfort in muscles of 1 or more extremity while in use, especially the upper extremities</td>
<td>New headache: new onset of or new type of localized pain in the head</td>
</tr>
<tr>
<td>Decreased brachial artery pulse: decreased pulsation of 1 or both brachial arteries</td>
<td>Temporal artery abnormality: temporal artery tenderness to palpation or decreased pulsation, unrelated to arteriosclerosis of cervical arteries</td>
</tr>
<tr>
<td>Blood pressure difference &gt; 10 mmHg between arms</td>
<td>Elevated erythrocyte sedimentation rate: erythrocyte sedimentation rate ≥ 50 mm/h by the Westergren method</td>
</tr>
<tr>
<td>Bruits over subclavian arteries or aorta: bruit audible on auscultation over 1 or both subclavian arteries or abdominal aorta</td>
<td>Abnormal artery biopsy: biopsy specimen with artery showing vasculitis characterized by a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells</td>
</tr>
<tr>
<td>Arteriogram abnormality: arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the proximal upper or lower extremities, not due to arteriosclerosis, fibromuscular dysplasia, or similar causes; changes usually focal or segmental ^ For purposes of classification, a patient shall be said to have Takayasu arteritis, if at least 3 of these 6 criteria are present. The presence of any 3 or more criteria yields a sensitivity of 90.5% and a specificity of 97.8%</td>
<td></td>
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^ For purposes of classification, a patient shall be said to have giant cell arteritis if at least 3 of these 5 criteria are present. The presence of any 3 or more criteria yields a sensitivity of 93.5% and a specificity of 91.2%
a result an ESR cutoff was not included in the classification for TAK but has become a key feature for GCA. However, heterogeneity among patients with LVV still needs to be considered. In particular, patients with GCA presenting with cranial features have a significantly higher acute phase response compared to those with either TAK or LV-GCA [5,20,23,24]. Future iterations of the ACR criteria for GCA may consider a lower ESR cutoff [22] and/or incorporate CRP because of a greater sensitivity [21,25]. Moreover, it appears that ESR and CRP are less reliable for determining disease activity in patients with TAK. Indeed, 23–44% of patients with TAK may have active vascular inflammation (based on histology at the time of surgery) despite normal inflammatory markers [26,27]. In isolation, acute phase reactants are unable to differentiate TAK from GCA. However, a high inflammatory response may indicate an increased likelihood of cranial arteritis in older patients. In the appropriate clinical context, a patient should undergo comprehensive evaluation for LVV with advanced imaging even if inflammatory markers are normal or only modestly elevated. Given that the currently available biomarkers are non-specific, further research is needed to identify serologic molecules for both diagnosis and monitoring of TAK and GCA.

**Clinical features and arterial symptoms**

Presenting symptoms in systemic autoimmune disease are relatively non-specific and can exhibit a high degree of commonality. Overall, constitutional symptoms are not reliable discriminators between TAK and GCA. Non-specific arthralgia and myalgia seen in 13–41% of patients with TAK can be difficult to distinguish from the symptoms of polymyalgia rheumatica that are characteristic of many patients with GCA [4,24]. While considered as a key criterion of GCA, new onset headache can also be observed in 45–52% of patients with TAK. On the other hand, the cranial features of scalp tenderness and jaw claudication are quite specific for GCA and occur infrequently in patients with TAK [4,20]. Ischemic ocular symptoms due to involvement of the posterior ciliary arteries are quite specific for GCA and occur infrequently in patients with TAK [4,20]. Vascular bruits tend to be more frequent in patients with TAK, particularly in the carotid region [4,24]. Nevertheless, carotid and subclavian bruits can be detected in approximately 30% patients with GCA. Similarly a discrepancy in brachial pulse, while more common in TAK, can be identified in 17–53% of patients with LV-GCA [4,17,24].

The majority of studies comparing the frequency of clinical features and arterial symptoms between TAK and GCA are limited to retrospective observational cohorts. As a result, detection and recording bias are undoubtedly present. Cranial features are likely preferentially noted in patients with GCA compared to TAK because they are not often considered features of the latter. Likewise, until recently, detailed examination of large artery involvement in GCA has not been consistently performed. As such, prospective studies with systematic evaluation of comprehensive vascular signs and symptoms in patients with TAK and GCA are needed to determine the degree of overlap present among these two conditions. One such prospective, longitudinal, observational cohort registering cases of TAK and GCA from 18 academic centers in the United States and Canada is ongoing [3].

**Distribution of arterial lesions**

Arteriographic abnormalities have long been the primary focus for identifying patients with TAK and have been included in both classification [15] and diagnostic criteria for this condition [12,13]. On the contrary, classification criteria for GCA did not evaluate arteriography as a potential variable [16]. The increased availability and use of non-invasive vascular imaging has provided recent insight into the extent and prevalence of large vessel involvement among patients with GCA. However, sub-clinical radiographic findings are more frequent than clinically detectable vascular manifestations and the impact of these findings on short and long-term disease outcomes remains unclear. Although some investigators have identified a higher rate of relapse among patients with LV-GCA [17], others have observed the contrary [23,28].

There is significant overlap in the distribution of arterial abnormalities seen in patients with TAK and GCA. Nevertheless, subtle differences exist and vascular territories with higher frequency of involvement vary depending on the cohort investigated [3,4,20,24] (table III). Although not consistent among all populations studied, patients with TAK tend to have more frequent lesions of the carotid and mesenteric arteries while GCA tends to have a predilection for the axillary arteries. Thoracic and abdominal stenotic changes are more commonly identified in patients...
with TAK while aneurysmal changes occur more frequently in GCA [4,24]. Even when the vascular abnormalities seen in patients with TAK are compared to those of patients with LV-GCA, significant differences emerge despite the often overlapping clinical phenotype (table III) [24]. Interestingly, Furuta et al. also identified that the length of the stenotic lesions in carotid and subclavian arteries may provide assistance in disease discrimination with long tapered-type lesions (median length 15 cm) present in GCA compared to short non-tapered-type lesions (median length 4.5 cm) in TAK [20].

It should be noted that in the study by Yoshida and colleagues [29] patients with LVV who did not fulfill criteria for GCA due to lack of cranial features, were labeled as TAK regardless of age. These groups were then divided into early-onset TAK (< 40 years) and late-onset TAK (≥ 40 years). Regarding location, carotid artery involvement was the only territory that differentiated early-onset TAK from late-onset TAK. In comparing frequency of stenosis and aneurysm in the thoracic and abdominal aorta, the former was seen with a higher rate in early-onset TAK and the latter in the older TAK group. These results parallel the findings differentiating TAK and GCA and highlight the similarities and near interchangeability of the terms "late-onset TAK" and "LV-GCA".

**Histopathology**

It is morphologically difficult to differentiate TAK from LV-GCA and several investigators note histopathologic findings to be largely indistinguishable [1,14,30,31]. The typical large vessel histopathologic findings in GCA are characterized by a lymphohistiocytic inflammatory infiltrate that originates in the vasa vasorum of the adventitia, penetrates the aortic wall, and migrates into the inner media and intima [32]. Inflammation can be segmental, circumferential, or transmural. Histiocytic multinucleated giant cells near the intima-media complex are frequently seen but not requisite for diagnosis. Medial necrosis resulting in loss of smooth muscle cells and collapse of the internal elastic lamina is a hallmark feature of aortic involvement and leads to the "tree bark" appearance grossly [32]. Intimal proliferation is more readily observed in temporal arteries but when present in the aorta is accompanied by a later dense fibrotic stage [33]. The intensity of the inflammatory infiltrate and the degree of fibrosis is quite variable and appears to be a function of the chronologic age of the disease [34]. Some features that are considered more characteristic of TAK include: a greater necrotizing and active neutrophilic inflammatory pattern, microabscesses, greater adventitial fibrotic thickening, and more well-formed granulomas [32,33]. While temporal artery biopsy can yield evidence of active inflammation in GCA, tissue biopsy and histology play little role in the diagnosis of TAK. This is because involved vessels are not amenable to sample; therefore histologic examination is typically only performed following revascularization surgery or autopsy [19]. As a result, although an abnormal arterial biopsy is a key feature for classification of GCA, histopathology has
been intentionally excluded from TAK classification and diagnostic criteria [12–15]. While arterial samples are sorely needed to understand better the underlying etiologic and pathogenic features of LVV, the increasing trend to diagnose LVV with imaging modalities may limit the availability of tissue specimens.

**Future directions**

While TAK and GCA share several commonalities, the classical forms of these conditions remain quite distinct. Despite their similarities, it is uncertain whether these diseases are indeed separate or part of a spectrum. Given the overlapping phenotypes, determining whether these diseases are derived from the same pathophysiologic origin will require studies focused on the biologic basis of disease. Significant advances in understanding the pathophysiology of GCA have occurred over the last decade [35]. On the contrary, less information is known about TAK, in part due to the lack of animal models and less readily available arterial tissue specimens. A notable difference between TAK and GCA includes the T-cell subset populations and the cytokine signatures present in the lesional tissue and peripheral blood. While both T helper 1 (Th1) and T helper 17 (Th17) cells appear to play a major role in LVV pathogenesis, in GCA Th17 cells and their associated cytokines are very glucocorticoid responsive but Th1 cells are resistant [36]. On the contrary, the opposite has been observed in TAK [37]. This may partially explain the pathophysiologic rationale why patients with TAK often respond to therapeutic agents (e.g. TNF inhibitors) that have demonstrated little efficacy in GCA. These findings may provide a foundation to understanding the pathophysiologic differences between TAK and GCA. However, such research is still in its infancy and needs to be confirmed in larger populations. In addition, future research will need to identify if the cellular and cytokine profiles of patients with extracranial/LV-GCA are more consistent with cranial GCA or TAK.

Even if classification criteria are not modified in the short term, collaborative efforts among vasculitis researchers are needed to agree on standardized terminology when describing patient populations. At current, a patient described in one center as late-onset TAK maybe labeled as LV-GCA in another. Some researchers have proposed expanding the classification of LVV into subgroups [31]. This process could provide further distinction among phenotypic subsets similar to criteria used for juvenile arthritis or spondyloarthropathies. A possible schematic is shown in figure 1.

With the advances in imaging, fewer temporal artery biopsies are being performed in older patients with radiographic evidence of LVV. As such, in addition to biopsy-proven cases, ongoing clinical trials for GCA are now including patients based on the presence of large artery inflammation detected with

**Figure 1**

Possible subgrouping of LVV based on distinctive features

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<table>
<thead>
<tr>
<th>Distinctive features:</th>
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<tbody>
<tr>
<td>Age at onset &lt; 40</td>
</tr>
<tr>
<td>Vascular signs and symptoms of the extremities</td>
</tr>
<tr>
<td>Large artery involvement confirmed by imaging</td>
</tr>
<tr>
<td>Frequency of arterial carotid, subclavian, aorta &gt;&gt; axillary</td>
</tr>
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</table>

**Takayasu arteritis**

<table>
<thead>
<tr>
<th>Distinctive features:</th>
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<tbody>
<tr>
<td>Age of onset ≥ 50</td>
</tr>
<tr>
<td>Absence of cranial symptoms</td>
</tr>
<tr>
<td>Vascular signs and symptoms of the extremities</td>
</tr>
<tr>
<td>Large artery involvement confirmed by imaging</td>
</tr>
<tr>
<td>Frequency of arterial involvement subclavian, axillary, aorta &gt;&gt; carotid</td>
</tr>
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</table>

**GCA Large-Vessel**

<table>
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<th>Distinctive features:</th>
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<tbody>
<tr>
<td>Presence of cranial symptoms</td>
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<tr>
<td>Transient or permanent vision loss</td>
</tr>
<tr>
<td>Histologic (or ultrasonographic) proof of temporal arteritis</td>
</tr>
<tr>
<td>Large artery involvement confirmed by imaging</td>
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**GCA Cranial & Large-vessel**

<table>
<thead>
<tr>
<th>Distinctive features:</th>
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<tbody>
<tr>
<td>Older individuals</td>
</tr>
<tr>
<td>Presence of cranial symptoms (new onset temporal headache, scalp tenderness, jaw claudication, temporal artery abnormality)</td>
</tr>
<tr>
<td>Histologic (or ultrasonographic) proof of temporal arteritis</td>
</tr>
<tr>
<td>Transient or permanent vision loss</td>
</tr>
<tr>
<td>Lack of large artery involvement on imaging</td>
</tr>
</tbody>
</table>
imaging (conventional angiography, non-invasive angiography or positron emission tomography) [38]. The inclusion of these patients and subsequent subgroup analyses will provide important information on how patients with LV-GCA differ from those with predominantly cranial manifestations.

The current classification criteria for TAK and GCA are insufficient and dated. The increased knowledge of these conditions over the last three decades has provided additional insight into genotypic differences as well as phenotypic overlap. A revision of classification criteria incorporating advanced imaging as well as addressing older patients with LVV and no cranial involvement is needed. Efforts are underway to develop and validate diagnostic and classification criteria for systemic vasculitides through the prospective collection of patient data [39]. This international collaborative effort has recruited over 5000 patients with either systemic vasculitis or a non-vasculitic disease with similar presentation features. Results from this study and the redesign of current criteria are eagerly awaited.

### Conclusion

In summary, TAK and GCA exhibit both striking similarities as well as distinct differences. Classifying classical forms of TAK and GCA is rarely the topic of debate. The greatest controversy surrounds understanding and classifying patients with LVV from age 40–50 years, as well as older individuals in whom cranial symptoms are absent. Current classification criteria are not sufficient for this population and limited information is known about this subgroup. Prospective clinical trials for GCA are currently enrolling patients diagnosed with LVV based on imaging. Analyses of outcomes compared to those with cranial GCA will be greatly anticipated. Efforts at updating the classification criteria for systemic vasculitides are ongoing and prospective data are being collected to assist in clarifying the phenotypic differences.

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none.

### Disclosure of interest

The authors declare that they have no competing interest.

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Classification of large vessel vasculitis: Can we separate giant cell arteritis from Takayasu arteritis?

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