REVIEW ARTICLE

Recent advances in the diagnosis and therapy of large vessel vasculitis

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ABSTRACT

Large vessel vasculitis (LVV), including Takayasu arteritis (TAK) and giant cell arteritis (GCA), causes granulomatous vascular inflammation mainly in large vessels, and is the most common primary vasculitis in adults. Vascular inflammation may evoke many clinical features including vision impairment, stroke, limb ischemia, and aortic aneurysms. The best way to diagnose LVV is to combine medical history, physical examination, various laboratory tests, and imaging modalities. Progress in imaging modalities facilitated early diagnosis and follow-up of the disease activity. Conventional angiography is no longer the gold standard for the diagnosis of TAK. Similarly, temporal artery biopsy is no longer the only tool for diagnosing cranial GCA. In selected cases, color Doppler ultrasound may be used for this purpose. Despite some similarities, TAK and GCA differ in many aspects and they are different diseases. They also have different clinical subtypes. The presence of aortitis does not always implicate the diagnosis of TAK or GCA; infectious aortitis, as well as noninfectious aortitis associated with other autoimmune rheumatic diseases should be excluded. Treatment of LVV includes glucocorticoids (GCs), conventional immunosuppressive agents, and biological drugs. Tumor necrosis factor inhibitors are ineffective in GCA but effective in TAK. On the other hand, tocilizumab may be used to treat both diseases. Promising targeted therapies evaluated in ongoing clinical trials include, for example, anti-IL-12/23 (ustekinumab), anti-IL-17 (secukinumab), anti-IL-1 (anakinra), anti-IL-23 (guselkumab), anti-cytotoxic T-lymphocyte antigen 4 (abatacept), Janus kinase inhibitors (tofacitinib and upadacitinib), anti-granulocyte/macrophage colony-stimulating factor (mavrilimumab), and endothelin receptor (bosentan) therapies.

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Introduction Large vessel vasculitis (LVV), including Takayasu arteritis (TAK) and giant cell arteritis (GCA), causes granulomatous vascular inflammation mainly in large vessels, and is the most common primary vasculitis in adults. Large vessels include the aorta, its major branches, extremity arteries, and analogous veins, according to the 2012 International Chapel Hill Consensus Conference nomenclature of vasculitis.[1] Briefly, the pathogenesis involves vascular inflammation and injury promoting intimal hyperplasia, adventitial thickening, and intramural vascularization, which impair the vessel integrity and tissue perfusion, and cause tissue ischemia.[2] This review aims to summarize recent advances in the diagnosis, differential diagnosis, and treatment of LVV.

General approach to diagnosis and classification of large vessel vasculitis The best way of diagnosing LVV is to combine medical history, physical examination, various laboratory tests, and imaging modalities. In active disease, elevated erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP) level, plus leukocytosis and thrombocytosis support the diagnosis of LVV. Strong acute phase response is in general more prominent in GCA than in TAK. However, normal ESR and CRP do not exclude the diagnosis of LVV. Leukopenia and thrombocytopenia are not expected in LVV, except in the case of immunosuppressive (IS) agent effect.[3,4]

Defined criteria are helpful but mainly serve as a background for the inclusion of patients into clinical trials. At the time when traditional

classification criteria of the American College of Rheumatology (ACR) for TAK and GCA were defined in 1990, only conventional angiography was available for vascular imaging.[5,6] Since then, considerable progress has been made in diagnostic imaging modalities for both diseases, including magnetic resonance angiography (MRA), computed tomography angiography (CTA), color Doppler ultrasonography (CDU), and positron emission tomography (PET) with 18F-fluorodeoxyglucose.[7-10] With respect to diagnostic imaging, conventional angiography is no longer the gold standard for the diagnosis of TAK. Similarly, temporal artery biopsy (TAB) included in the 1990 ACR criteria for GCA, is no longer the only tool for diagnosing GCA, and there is a growing tendency to use CDU for diagnosing temporal arteritis. For these reasons, it became necessary to develop new classification criteria, including new imaging modalities. The DCVAS (Diagnostic and Classification Criteria for Vasculitis Study) project included TAK and GCA, and the first draft data were presented at the 19th International Vasculitis and ANCA Workshop held in Philadelphia in 2019 but have not been published yet.

Prominent clinical features of Takayasu arteritis TAK presents with different symptoms and clinical findings, depending upon the duration and phase of the disease. The first phase is characterized by nonspecific constitutional inflammatory symptoms, including fever of unknown origin (FUO). The second phase is characterized by vascular mural inflammation. Involvement of carotid arteries may cause carotidynia and neck pain. Similarly, inflammation in the thoracic aorta may cause dorsal pain. In the late phase of the disease, severe narrowing or occlusions may occur mainly in the proximal parts of the arterial branches originating from the aortic arch. Decreased or absent upper extremity pulses, with or without discrepant measurements of arterial blood pressure between the upper extremities, arterial bruits, and intermittent extremity claudication are among typical features of late stage TAK. Severe hypertension may be caused by atypical coarctation of the aorta, loss of vascular compliance, aortic valve regurgitation due to aortitis, or renal artery stenosis.

Recently, 5 typical clinical patterns have been described. The most frequent type includes patients with vascular-related symptoms (46%), encompassing limb claudication, cranial symptoms, angina, and abdominal claudication. Other types include major ischemic events (29%), carotid artery tenderness (15%), nonspecific constitutional symptoms (8%), and asymptomatic patients (3%).[11]

Angiographic classifications and heterogeneity of Takayasu Since the location and extent of vessel involvement determine the disease severity, there have been attempts to classify patients with TAK according to the involved vessels, based upon angiographic findings. The Numano's classification was most commonly used for this purpose, and it grouped patients into 6 subtypes based on the involvement of the aortic arch, aortic arch branch vessels, and ascending aorta, thoracic aorta, abdominal aorta, and renal arteries. Despite its usefulness in demonstrating ethnic and geographic differences in arterial lesion distribution among patients with TAK, there were also limitations including suboptimal differentiation of patients and a lack of convincing prognostic clinical value.[12]

Recently, Goel et al[12] have developed a novel classification system defining 3 clusters in TAK, based on the distribution of arterial lesions. The patients in the first cluster had significantly more advanced disease in the abdominal aorta, and renal and mesenteric arteries. These patients were more likely to have renal hypertension and mesenteric ischemia, and were younger at the time of the disease onset. The patients in the second cluster had significantly more advanced bilateral disease in the carotid and subclavian arteries, and were more likely to have a history of stroke and carotidynia. Achieving clinical remission was difficult in these patients. The third cluster consisted of patients with an asymmetric, focal disease with fewer involved territories. These patients were less likely to have an occlusive and damaging disease.[12]

How to diagnose Takayasu arteritis earlier For early diagnosis, a clinician should consider the possibility of TAK in a young patient with persistent systemic inflammation, especially in the presence of red flags that include carotidynia, hypertension, angina pectoris, vertigo and syncope, extremity claudication, absent / weak peripheral pulses, discrepant blood pressure in the upper limbs (>10 mm Hg), arterial bruits, and aortic regurgitation.[13] In suspected cases, the second step is to confirm the diagnosis of TAK by appropriate imaging methods. EULAR recommends the use of MRA as the first choice to investigate mural inflammation and / or luminal changes to confirm the diagnosis of TAK.[7] Fluorodeoxyglucose positron emission tomography / computed tomography (FDG-PET/CT) scan and / or CDU may be used as alternative imaging modalities in patients with suspected TAK. CDU is of limited value for the assessment of the thoracic aorta.

Clinical features of giant cell arteritis GCA is usually seen in patients older than 50 years and is often associated with polymyalgia rheumatica. It is not difficult to diagnose GCA in the presence of a new onset headache, claudication of the jaw or tongue, and temporal artery abnormalities associated with a systemic inflammatory syndrome and proximal muscle pain in elderly patients. Likewise, acute ocular symptoms such as impaired vision, diplopia, and amaurosis fugax should suggest the possibility of GCA.[2] Ophthalmological emergencies generally result from anterior ischemic

optic neuropathy due to occlusion of the posterior ciliary arteries. Older patients who had unilateral permanent visual loss at diagnosis have a higher risk of new ischemic visual loss during treatment than the other patients.[14]

However, those well known features represent mainly the cranial subgroup of GCA (C-GCA). GCA may also present with large vessel involvement (LV-GCA) without cranial arteritis, or only with FUO. Besides, atypical presentations may also occur in C-GCA. Although the involvement of vertebral and internal carotid arteries is not common, there may be rare cases presenting with stroke.[15] GCA may rarely cause brachial diplegia ("man-in-a-barrel" syndrome), characterized by weakness of the upper extremities sparing the trunk and lower limbs.[16]

Different subgroups of giant cell arteritis Patients with GCA may be divided into 4 different subsets, based on the presence or absence of temporal arteritis and large vessel involvement (LVI).[17]

1 C-GCA: Patients with only cranial arteritis, with high burden of symptoms of cranial ischemia and visual changes.

2 LV-GCA: Patients without cranial arteritis and only LVI, with high burden of upper extremity vascular abnormalities, and constitutional and pulmonary symptoms. Visual disturbances are rare in this group.

3 Patients with evidence of both C-GCA and LV-GCA are older with a high prevalence of symptoms of cranial ischemia, plus vascular abnormalities, bruits, constitutional symptoms, and high acute phase reactants.

4 There may be some patients with no evidence of C-GCA or LV-GCA but presenting with notable morning stiffness and leg claudication.

On the other hand, there are 2 more different subgroups of GCA in terms of severity of the systemic inflammation. The first subgroup is mainly characterized by severe systemic inflammation, while in the second subgroup, there is less inflammation but a prominent vaso-occlusive process can be noted. Acute vision loss is generally seen in the second subgroup.[18-20]

In general, the main acute complication of GCA is visual loss, which can become permanent in 15%–20% of patients. Conversely, the main long-term complications are cardiovascular events including thoracic aortic aneurysms and dissections, ischemic heart disease, myocardial infarction, and peripheral vascular disease.[21] Rarely, nonproductive cough, sore throat, hoarseness, and even interstitial lung disease may also be seen in GCA.[22]

Diagnosis of giant cell arteritis In C-GCA, TAB showing mononuclear cell infiltrate or granulomatous inflammation remains the gold standard, however, imaging of the superficial temporal arteries with CDU is an alternative diagnostic method.[23] When TAB is performed, the artery specimen should be at least 1 centimeter long to avoid missing inflammatory segments of the vessel.[24] Whether TAB should be made unilateral or bilateral is controversial. Many clinicians perform unilateral biopsy initially, and make a contralateral biopsy only if the initial biopsy is negative. It was reported that performing bilateral TAB increased the diagnostic sensitivity by up to 12.7%, as compared with unilateral TAB.[25] If the patient needs urgent glucocorticoid (GC) treatment, such as in the presence of an ophthalmic emergency, the treatment should not be delayed. Fortunately, TAB remains a valuable diagnostic procedure even after several weeks of GC treatment.[26]

As an alternative to TAB, CDU may evaluate not only temporal artery, but also carotid, axillary, and femoral arteries, by visualizing luminal changes, stenosis, and aneurysms. CDU may detect the characteristic, homogeneously thickened vessel wall and mural inflammation in the presence of vasculitis. The hypoechoic area surrounding the lumen of the artery is called a "halo sign", and represents edema and vascular inflammation of the arterial wall. When tested against positive TAB in GCA, sensitivity of CDU for detecting abnormalities such as the halo sign is 77%, while specificity may reach up to 96%.[23]

As also recommended by both the European Alliance of Associations for Rheumatology (EULAR) and the British Society for Rheumatology (BSR), the use of fast-track clinics may permit prompt diagnosis and treatment within 48 hours. GCA pretest probability score may be helpful to determine which patients should be referred. According to EULAR, CDU of cranial and supraaortic arteries should be the initial evaluation.[7,23,37] MRA may also be tried, if CDU is not available.[7] TAB is advocated if CDU or MRA are not available or the results are inconclusive. Unlike EULAR, BSR guidelines recommend either CDU or TAB as primary diagnostic modalities in C-GCA, while MRA is recommended if CDU and TAB are not available.[27]

Both EULAR and BSR do not recommend using CT/CTA or PET-CT as the first diagnostic imaging option in patients with suspected C-GCA. The main disadvantages of PET-CT include patient exposure to radiation, sensitivity to GC treatment, and high cost.[7,23,27]

The BSR guidelines for diagnosing GCA are as follows [27]:

1 If the probability is below 20% and CDU is negative, TAB is not recommended. An alternative diagnosis should be considered.

2 If the probability is below 20% and CDU is positive, TAB is recommended for diagnosis.

3 If the probability is between 20% and 50% and CDU is equivocal, TAB is recommended for diagnosis.

4 If the probability is above 50% and CDU is negative, TAB is recommended for diagnosis.

5 If the probability is above 50% and CDU is positive, GCA can be diagnosed without TAB.

In summary, TAB is generally recommended in patients with an uncertain pretest probability or in whom CDU fails to confirm the diagnosis.[27]

The TABUL study (Temporal Artery Biopsy vs Ultrasound in Diagnosis of Giant Cell Arteritis) is an excellent multicenter, prospective study that compared CDU and TAB in new cases of suspected GCA.[28] CDU was reported to have superior sensitivity over TAB (54% vs 39%), but inferior specificity as compared with the clinical diagnosis of GCA as the reference standard (81% vs 100%).

Unfortunately, the halo sign seen in CDU is not pathognomonic for GCA. Antineutrophil cytoplasmic antibody–positive vasculitis, classic polyarteritis nodosa, angiolymphoid hyperplasia with eosinophilia, multiple myeloma, non-Hodgkin lymphoma, atherosclerosis, amyloidosis, infections, and migraine may also cause a falsely positive halo sign in CDU of the temporal artery.[29] In such cases, TAB is used for final diagnosis.

Differences in the involved arteries between Takayasu and giant cell arteritis The type of aortic involvement and distribution of the involved arteries are different. TAK presents a tendency for stenotic aortic lesions, while thoracic aneurysmal dilatation is more common in GCA. The left subclavian artery together with bilateral carotids, branches of the internal carotid artery, renal and mesenteric, and to a lesser extent, pulmonary artery, are involved in TAK. On the other hand, bilateral (symmetric) subclavian and axillar arteries and branches of the external carotid artery are more commonly involved in GCA.[17,30]

Approach to the patient with aortitis Aortitis is a group of disorders characterized by the inflammation of the aorta and is related to significant morbidity and mortality through the development of an aortic aneurysm, aortic wall rupture, and aortic acute dissection, or thrombotic luminal obstruction. Various infectious, noninfectious, and autoimmune conditions may cause aortitis. Initially, the possibility of infectious aortitis should be excluded using standard microbiological diagnostic tests. Although the most common causes of noninfectious aortitis are TAK and GCA, aortitis may also be associated with other autoimmune rheumatic diseases, such as rheumatoid arthritis, spondyloarthropathies, psoriatic arthritis, Behcet's disease, Cogan's syndrome, relapsing polychondritis, systemic lupus erythematosus, Sjögren's syndrome, antineutrophil cytoplasmic antibody–associated vasculitis, sarcoidosis, inflammatory bowel diseases, and IgG4-related disease. Iatrogenic aortitis may also occur due to medications, such as granulocyte colony-stimulating factor and checkpoint inhibitors. Finally, aortitis may also be isolated, as included in the group of single organ vasculitis in the revised Chapel Hill classification. Therefore, in the presence of aortitis, the diagnosis of TAK or GCA may be made after excluding all of these possibilities.[20,31]

Differentiating atherosclerosis from vasculitis Among pathologies affecting the aorta and its branches, atherosclerosis is probably the most common mimicker of LVV, especially in older patients. Association between inflammation and atherosclerosis is well known, and they may be present together. Given that atherosclerosis is also an inflammatory process, atherosclerotic plaques may show increased uptake of gadolinium contrast in MRA and increased FDG uptake in PET-CT imaging, resulting in further confusion in the differential diagnosis. Unfortunately, the halo sign with CDU may also be seen in atherosclerosis.[32]

Atherosclerosis may also mimic isolated aortitis, which is not a benign process.[33,34] Isolated aortitis is seen predominantly in men and younger patients than GCA. The aortic arch, thoracic and abdominal aortas are involved, while aortic branches seem to be spared.[35]

Recently, it has been reported that among various imaging findings, high intensity and diffuse uptake patterns on FDG-PET/CT showed the highest specificity in distinguishing LVV from atherosclerosis. Besides, CTA may also be useful in detecting increased calcification in atherosclerotic plaques. In the presence of noncalcified plaques, morphological vessel wall abnormalities may also be helpful. Eccentric and focal thickening of the arterial wall favors atherosclerosis, while concentric thickening and stretching in a long segment of an artery favors vasculitis.[32]

Other practical points to help differentiate atherosclerotic lesions from vasculitic lesions include their localization in bifurcation sites and ostiums, rather than in proximal parts of the arteries. Atherosclerotic aortic aneurysms are generally abdominal (mostly infrarenal), rather than thoracic. Another clinical pearl is that upper limb arteries are rarely involved in atherosclerosis, unlike in LVV.[20]

Management of Takayasu arteritis and giant cell arteritis **General approach and principles** Pharmacological treatment of LVV includes remission induction (suppressing initial vascular inflammation) and maintenance of remission. In general, evidence-based treatment is more robust for GCA, while there are fewer randomized clinical trials (RCTs) for TAK.

Glucocorticoids (GCs) are certainly the cornerstone of treatment and high-dose GCs remain the gold standard for remission induction in the active disease. GCs are more effective for inhibiting the Th-17 response, reducing anemia, systemic symptoms, acute inflammatory response, and systemic inflammation. However, there are 2 issues related to their use. First, GCs are not as effective in suppressing the Th-1 cell network responsible for long-term vascular complications.[36] Second, well known adverse effects of GCs cause problems. Nearly 47% patients treated with GC monotherapy tend to relapse during dose tapering, leading to long-term treatment with high cumulative GC exposure.[37]

For these reasons, adjunctive IS treatments and biologic agents have been proposed

as add-on therapies, mainly for GC-sparing effects.[38,29]

Methotrexate (MTX) is the most popular among IS agents used for GCA treatment. A meta-analysis of 3 randomized placebo-controlled MTX trials reported lower relapse rates, lower cumulative GC doses, and a higher rate of GC-free remission.[40] Although MTX is generally a well tolerated and safe medication, potential toxicity in the elderly should be considered, especially if there is an associated impairment in renal function. Data for azathioprine (AZA), cyclophosphamide (CYP), and leflunomide (LEF) are limited. Since they failed to demonstrate a significant favorable benefit/risk ratio, conventional IS agents other than MTX are not recommended for GCA treatment.[36,41]

Unlike in TAK, tumour necrosis factor inhibitors (TNFi) remained ineffective in clinical trials for GCA treatment.[42-44] Tocilizumab (TCZ), an anti-interleukin 6 (IL-6) receptor inhibitor is currently the most widely used and effective GC-sparing biologic agent used for GCA. The efficacy and safety of TCZ for the treatment of both newly diagnosed and refractory/relapsing GCA have been demonstrated in 2 randomized, double blind, placebo controlled trials.[45,46] TCZ was shown to reduce the total number of relapses and the cumulative dose of GCs, without increasing serious adverse effects.

In a recent Spanish multicenter, retrospective, real-life, observational study,[47] the efficacy of TCZ was confirmed in 134 refractory GCA patients, despite their older age, longer disease duration, higher ESR values, and greater use of IS agents. However, the rate of serious infections was reported to be higher than in the GIACTA (Giant Cell Arteritis Actemra) trial.

Abatacept is a fusion protein comprising cytotoxic T cell antigen 4 and the Fc region of IgG1 that inhibits CD28-mediated T cell costimulation. Initial data showed that relapse-free survival in GCA patients at 12 months was slightly higher in the abatacept group than in the placebo group.[48] Similarly, mavrilimumab, which is a fully humanized monoclonal antibody targeting the GM-CSF receptor α subunit, was tested in a phase II study. Initial data were promising with regard to GC sparing effect and sustained disease remission. The main advantage over TCZ was that acute phase reactants retained their clinical value under mavrilimumab treatment. Further data are awaited both for abatacept and mavrilimumab.

On the other hand, contrary to GCA, there are more alternatives serving as GC-sparing adjunctive treatments for TAK. The effective IS agents are MTX, LEF, AZA, MMF, and CYP.[49-51] Despite the lack of RCTs supporting their efficacy, TNFi agents are widely used in clinical practice for TAK patients with refractory disease, based on case series and expert opinion.[50,52-54]

The efficacy of TCZ was tested in a randomized controlled TAKT (Takayasu Arteritis Treated with Tocilizumab) trial.[55] Although the primary end point (time to relapse) did not reach statistical significance between the treatment arms, there were favorable trends and no safety concerns were raised. Extended follow-up of this trial, further observational studies, and case series supported the sustained benefit of TCZ in TAK.[53,56,57] According to retrospective analyses, biologic therapies lead to better outcomes in patients with TAK than conventional IS agents.[52-54] However, abatacept was not found effective in TAK, unlike in GCA.[58]

Guidelines for treatment of large vessel vasculitis

Although there are many guidelines for the treatment of LVV, the 2018 update of the EULAR recommendations,[59] BSR guidelines,[27] and 2021 ACR guidelines[60] merit special attention with some differences to be discussed.

According to the guidelines, as soon as the diagnosis is made, high-dose GC therapy (40–60 mg/day prednisone-equivalent) should be initiated immediately for induction of remission in active GCA or TAK. Dosing GC according to body weight, alternate day administration of oral GC, splitting the GC dose into 2 or more daily doses, and using modified-release tablets are not recommended in the guidelines. Only if GCA-related visual symptoms are present, initial intravenous (IV) pulse GC treatment is recommended. Once the disease is controlled, EULAR recommends tapering the GC dose to a target dose of 15–20 mg/day within 2–3 months. At the end of the first year, targeted maintenance dose is lower for GCA (≤5 mg/day) than for TAK (≤10 mg/day).

EULAR recommends adding adjunctive therapy for GCA patients only in the presence of refractory or relapsing disease, or in the presence of increased risk of GC-related adverse effects or complications. Since TNFi treatment is not effective in GCA, TCZ is the first choice for such patients, while MTX may be used as an alternative. EULAR claims that substantial number of patients with GCA treated with GC monotherapy do not relapse during dose tapering. EULAR states that the decision to use adjunctive IS therapy should be individualized, based upon the balance between potential complications of GC vs TCZ.

Since high disease activity and extent at the disease onset appear to be associated with a more severe and more prolonged disease course in GCA, such patients, particularly with an active extracranial disease, might benefit from early adjunctive GC-sparing treatment, which permits more rapid GC dose reduction.

Since TAK usually has a more chronic and relapsing disease course, treatment approach for TAK differs with respect to the adjunctive therapy. GC monotherapy is less effective and GC dose tapering should be slower in TAK due to the greater tendency for relapse. Therefore, EULAR recommends adjunctive IS agents initially in combination with GCs in all patients with TAK, unlike in GCA. EULAR also recommends the use of either

TABLE 1 Ongoing studies on treatment of Takayasu arteritis and giant cell arteritis

Investigated drugs	Disease/study (https://clinicaltrials.gov)
Takayasu arteritis (TAK)	
Leflunomide (LEF)	2 studies: the first investigates the efficacy and safety of LEF in patients with active TAK, and the second (ECTA-cohort study) investigates the effectiveness of LEF and TCZ in TAK.
Ustekinumab	This placebo-controlled study of ustekinumab addresses the efficacy in patients with relapsing TAK.
Cyclophosphamide (CYP)	2 ongoing studies: one is a phase 2–3 study investigating the efficacy of CYP + GC therapy in patients with active TAK. The other compares the efficacy and safety of GC + MMF +MTX vs GC + CYP followed by GC + AZA for the treatment of active TAK.
Infliximab (IFX)	3 ongoing studies: the first one addresses the effectiveness of IFX in patients with active TAK, the second addresses the effectiveness of biosimilar IFX in TAK patients, and the third multicenter, randomized, prospective study evaluates the efficacy and safety of IFX vs TCZ in refractory or relapsing TAK.
Janus kinase (JAK) inhibitors	3 ongoing studies: the first study compares the efficacy of tofacitinib with MTX, the second compares the efficacy of tofacitinib with adalimumab, and the third addresses the efficacy of upadacitinib in combination with GC.
Tocilizumab (TCZ)	A multicenter, randomized, prospective study compares the efficacy and safety of IFX versus TCZ in refractory/relapsing TAK.
Upadacitinib	A phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of upadacitinib in subjects with TAK (SELECT-Takayasu).
Giant cell arteritis (GCA)	
Tocilizumab	11 studies: focusing on pharmacodynamics, pharmacogenetic and safety, effectiveness in cerebral-vascular involvement, comparing the effectiveness of MTX vs TCZ in acute anterior ischemic optic neuropathy, dose tapering of TCZ in combination with GCs.
Sirakumab	Efficacy and safety of sirakumab (a human anti-IL-6 monoclonal antibody) in GCA.
Ustekinumab	2 studies addressing the effectiveness of treatment and treatment of relapses in refractory GCA.
Secukinumab	2 ongoing studies on the pharmacodynamics and safety of secukinumab in GCA.
Guselkumab	A study addressing the efficacy of guselkumab (a selective IL-23 inhibitor) vs placebo for tapering GC dose.
Baricitinib	A single open-label pilot study assessing the safety and tolerability of baricitinib with standardized GC tapering.
Upadacitinib	A single study addressing the safety and efficacy of upadacitinib in GCA.
Anakinra	Addition of anakinra to GC for decreasing the GCA relapse rate.
Bosentan	Treatment of sudden blindness due to anterior ischemic optic neuritis with endothelin inhibitor bosentan, despite the administration of GCs.
Hydroxychloroquine	A multicenter, double-blind, controlled trial to assess the GC sparing effect of HCQ in non-complicated GCA.
Abatacept	3 studies on the efficacy and safety of abatacept treatment in newly diagnosed or relapsing GCA.

Abbreviations: AZA, azathioprine; GC, glucocorticoid; HCQ, hydroxychloroquine; MMF, mycophenolate mophetil; MTX, methotrexate

TCZ or TNFi agents in the case of relapsing or refractory disease despite conventional IS agents. Multicenter studies from France and Turkey compared TCZ and TNFi agents in TAK and found no difference in their effectiveness.[61,62]

In the case of a major relapse of both TAK and GCA, EULAR recommends reinstitution or dose escalation of GC therapy as recommended for new-onset disease. For minor relapses, an increase in GC dose at least to the last effective dose is recommended. Initiation or modification of the adjunctive therapy should be considered especially after the recurrent disease relapses.[59]

The ACR 2021 guidelines offer considerable differences related to GC doses and the role of TCZ in early GCA treatment.[60] The ACR recommends that moderate-dose GC may be used in patients with a significant risk of severe GC toxicity and patients with a low risk of vision loss or other life- or organ-threatening complications. The addition of TCZ as a GC-sparing agent for the initial treatment of GCA is conditionally recommended in selected cases, unlike in the EULAR guidelines. The ACR also offers MTX or abatacept as alternative GC-sparing agents for patients unable to use TCZ. According to the ACR, in the presence of inflammation in a new vascular territory or progression of existing vascular lesions with imaging, treatment should be escalated only if there are also symptoms and signs of the active disease.[60]

Antiplatelet or anticoagulant therapy should not be routinely used for the treatment of LVV, unless it is indicated for other reasons such as coronary heart or cerebrovascular disease.[59] However, cardiovascular disease risk due to chronic low-grade inflammation and prolonged GC exposure should always be considered in the management of LVV. Additional risk factors such as hypertension, diabetes, and hypercholesterolemia, all of which are intensified by GCs, should also be treated according to standard guidelines. For patients with GCA, who have critical or flow-limiting involvement of the vertebral or carotid arteries, ACR conditionally recommends adding low-dose aspirin. Despite younger age at the disease onset, TAK patients also suffer from cardiovascular disease, and frequency of carotid atherosclerotic plaques was found to be increased in patients with TAK as compared with healthy controls.[63]

As a general rule, elective endovascular interventions or reconstructive surgery should be performed when the disease activity is suppressed, unless there are urgent problems including arterial vessel dissection or critical vascular ischemia.[59]

Problems with tocilizumab and need for other treatments Although TCZ plays an important role in the treatment for both GCA and TAK, particularly with active and relapsing disease, there are many questions including the length of treatment and monitoring the disease activity. Since TCZ suppresses IL-6 dependent fever and acute phase reactants including ESR and CRP, this may mask the diagnosis of possible infections.[64] Besides, despite clinically quiescent disease and suppressed systemic inflammation, histologically active vasculitis may be present.[65] Whether early TCZ monotherapy following 3 IV pulses of GC may induce the remission was recently investigated in an open-label study. However, based on limited data from this study, such an approach is not currently recommended.[66]

Potential agents for future treatment of large vessel vasculitis Promising targeted therapies evaluated in ongoing clinical trials include, but are not limited to, anti-IL-12/23 (ustekinumab), anti-IL-17 (secukinumab), anti-IL-1 (anakinra), anti-IL-23 (guselkumab), anti-cytotoxic T-lymphocyte antigen 4 (abatacept), Janus kinase inhibitors (tofacitinib and upadacitinib), anti-granulocyte / macrophage colony-stimulating factor (mavrilimumab), and endothelin receptor (bosentan) therapies. Some of these ongoing trials are summarized in **TABLE 1** (https://clinicaltrials.gov).

There are also some case series and noncontrolled small studies reporting satisfactory responses to ustekinumab,[67,68] rituximab,[69] and Janus kinase inhibitors[70] in patients with TAK, although overall data are limited.

ARTICLE INFORMATION

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