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Large Vessel Vasculitis

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ABSTRACT

Large vessel vasculitis (LVV) manifests as inflammation of the aorta and its major branches, and is the most common primary vasculitis in adults. Although comprised of only two distinct conditions, giant cell arteritis (GCA) and Takayasu arteritis (TAK), the phenotypic spectrum of primary LVV is complex. Non-specific symptoms often predominate and so patients with LVV may present to different healthcare providers and settings. Rapid diagnosis, specialist referral and early treatment are key to good patient outcomes. Unfortunately, disease relapse remains common and chronic vascular complications are a source of significant morbidity. The ability to accurately monitor disease activity remains challenging and recent progress in both vascular imaging techniques and laboratory biomarkers may facilitate better matching of treatment intensity with disease activity. Advances in pathophysiological understanding have paved the way for novel biologic treatments which target important mediators of disease in both GCA and TAK. Such work has highlighted the significant heterogeneity present within LVV and the importance of an individualized therapeutic approach. Future work will focus on understanding the mechanisms behind persisting vascular inflammation which will inform the development of increasingly sophisticated imaging technology. Together, these will allow better disease prognostication, limit treatment-associated adverse effects, and facilitate the development and use of novel therapies in a more targeted way.

1. INTRODUCTION

Inflammation of large blood vessels, such as the aorta and its main branches, can occur due to a range of infectious, inflammatory, and immune diseases (**Table 1**). However, it most commonly presents as one of the two primary large vessel vasculitides – giant cell arteritis (GCA) or Takayasu arteritis (TAK).[1] These conditions are the focus of this Primer and defined as large vessel vasculitis (LVV) from here on.

First described almost 100 years ago, GCA – an idiopathic inflammatory condition characterized by granulomatous arteritis in temporal artery biopsy (TAB) specimens – was commonly referred to as 'temporal arteritis'.[2] Later, it was observed that those with this condition often developed constitutional symptoms and features of extravascular inflammation attributed to an overlap with the more common polymyalgia rheumatica (PMR).[3] Several autopsy series had also noted arteritis within the aorta and other great vessels.[4, 5] Rapid improvements in vascular imaging since the beginning of the 21st century have allowed an even better understanding of the extent of large vessel involvement[6, 7] and it is now recognized that GCA encompasses a broad phenotypic spectrum of medium and large artery inflammation. Nomenclature has evolved to reflect this, with the terms 'large vessel-GCA' (LV-GCA), 'cranial-GCA' (C-GCA), and 'LV-GCA with cranial involvement' now suggested (**Figure 1**).[8]

TAK was first described in 1908 as a series of retinal vascular abnormalities by Japanese ophthalmologist Mikito Takayasu and colleagues.[9] The association with absent or diminished peripheral pulses led to the term 'pulseless disease', and autopsy studies demonstrated a pan-arteritis involving the aorta and major branches.[10] Although early descriptions of the disease involved those of Japanese origin, TAK is now recognized to occur worldwide.

In general, GCA and TAK are defined by granulomatous inflammation of the blood vessel wall, and a maladaptive immune response to injury that promotes intimal hyperplasia, adventitial thickening, and intramural vascularization which ultimately threaten vessel integrity and tissue perfusion. Recent advances in the cellular and molecular analysis of inflammatory lesions in LVV have translated into improved pathogenic understanding and mechanism-based diagnostic and therapeutic approaches that are increasingly tailored to the needs of the individual patient. These treatments are being evaluated in more complex and sophisticated clinical trials, and the need for guidance on their use has driven exciting advances in vascular imaging.

Disease outcomes in LVV are generally better than in most systemic inflammatory conditions, including small vessel vasculitis. However, LVV is not benign. Constitutional symptoms such as fatigue, fever and weight loss are common and disabling. Clinical manifestations of arterial narrowing include vision loss and stroke in the short-term, and limb ischemia and heart failure in the longer-term. Risk of aortic aneurysm formation and rupture is also increased. Additionally, the consequences of prolonged immunosuppression are significant, including increased risks of cardiovascular disease and infection. Although improved treatment strategies allow many patients to achieve disease remission, relapse is common. Those with LVV may present to a range of medical or surgical specialties and require inter-disciplinary management. As such, a working knowledge of current nomenclature, diagnostic approaches and therapeutic options is essential to providing good care to these patients. This Primer provides an in-depth, global review of the epidemiology, pathophysiology, diagnosis, and management of LVV and highlights areas where ongoing and future research may be most impactful.

2. EPIDEMIOLOGY

Disease incidence

GCA is the most common primary vasculitis worldwide, although precise estimates of incidence vary with the criteria used for case definition (e.g. histologically-defined disease based on TAB, classification criteria-defined disease, or diagnostic coding). It occurs almost exclusively in those aged >50 years, and the incidence increases with age to peak in the eighth decade, where there is a 40-fold increased risk compared to those aged 50-59.[11-13] Females are more commonly affected than males, at a ratio of approximately 3:1.[12-15] LV-GCA patients are younger at presentation, are more commonly female, and more often present with bilateral arterial involvement when compared with C-GCA.[16, 17]

There is significant global variation in GCA incidence, with estimates as high as 20-44/100,000 (aged >50 years) in Northern Europe, and as low as ~1.5/100,000 in Southeast Asia (**Figure 2**).[14, 18-20] Similarly, the incidence within Europe shows a marked north-south gradient, and is reported to be <10/100,000 persons over the age of 50 in Mediterranean populations.[11, 19] There is a particular predilection amongst those of Scandinavian ancestry, both within Northern Europe and in Americans of Scandinavian descent, suggesting shared genetic risk. Conversely, a lower reported incidence in Finland may reflect the distinct genetic ancestry in this population compared with Scandinavia.[21] GCA is thought to be even less common in African, Asian and Arab countries. However, formal epidemiological data in these populations are limited, which may reflect a combination of lower disease burden, differences in access to healthcare (and thus diagnosis), or lack of study in developing countries.

In Japan, where it was first described, TAK has an estimated annual incidence of 1-2/million.[22] In Europe, the annual incidence ranges from 0.4 to 3.4/million.[23-26] Age of onset is usually between 10 to 40 years, and is the major epidemiological feature that distinguishes TAK from GCA, although late-onset TAK is increasingly recognized.[27] It is also more common in women, who account for 80-90% of cases in Europeans.[28] The sex ratio, however, is less skewed towards females in China, India and Thailand (where it ranges between 3-4:1), implicating a potential role for regional environmental factors or genetics in pathogenesis.[29-31] A study in Japanese patients also suggests a shift in sex ratio towards males in recent times.[32] Notably, the pattern of disease may differ between young- and late-onset disease, and between males and females. Renal artery involvement, active disease with constitutional symptoms and major ischemic events (such as myocardial infarction, renovascular hypertension, stroke) are more common in younger patients.[30, 33, 34] Involvement of the thoracic aorta and its branch vessels leading to upper limb claudication and pulse loss seems to be more common in females, whereas the renal and iliac arteries are more commonly affected in males.[31, 35]

Disease determinants & risk factors

The geo-ethnic variation in GCA incidence suggests a significant genetic contribution to disease etiology. An MHC class II association has been recognized for some time, in particular with *HLA-DRB1*04* alleles.[36] Other studies have described links with genes encoding cytokines and their receptors (e.g. tumour necrosis factor (TNF)[37]), molecules associated with endothelial function (e.g. intercellular adhesion molecule 1 (ICAM-1)[38], vascular endothelial growth factor (VEGF)[39]), and regulators of both innate and adaptive immunity (e.g. Toll like receptor 4 (TLR-4)[40], *PTPN22*[41]). However, it was only recently that the first large genome-wide association study (GWAS) in GCA, including >2,000 subjects of European ancestry, confirmed a strong HLA class II association.[42] This is compatible with an underlying antigen-driven immune response in disease pathogenesis, and the predominance of $CD4^+$ T cells within inflammatory lesions. This study also identified risk polymorphisms in *PLG* (encoding plasminogen) and *P4HA2* (encoding an isoform of the alpha subunit of collagen prolyl 4-hydoxylase; essential for collagen biosynthesis), compatible with alterations in vascular remodelling in disease susceptibility.

In contrast to the class II association observed in GCA, disease susceptibility and severity in TAK is consistently associated with inheritance of the *HLA-B*52:01* allele in populations of multiple ethnicities.[43] Of note, the inflammatory lesions in TAK include a large number of $CD8^+$ T cells, which are restricted by HLA class I polymorphisms.[44, 45] Several large-scale genetic studies in the last decade have identified additional HLA and non-HLA susceptibility loci in ancestrally diverse populations,[44, 46-49] which implicate a variety of pro-inflammatory, regulatory immune response, and humoral pathways in disease pathogenesis. Susceptibility factors common to both GCA and TAK have also been suggested, primarily within the *IL12B* locus. *IL12B* encodes the p40 subunit, which is shared between IL-12 and IL-23, known to function as lineage-inducing cytokines for Th1 and Th17 cells.[50]

Reports of seasonal variation in GCA onset suggest that environmental factors may trigger disease in genetically susceptible individuals.[51] In particular, significant effort has gone towards identifying possible infectious triggers. Small epidemiological, clinical, and molecular studies have described associations with a variety of organisms, including varicella zoster virus, Chlamydia *pneumoniae*, Mycoplasma *sp.* and parvovirus B19. [52] However, it is unsurprising for an elderly host to have encountered several infections, and for there to be deposition of microbial products in tissue. These findings do not prove causality for large vessel inflammation, and there is no consistent evidence of any particular micro-organism as a direct trigger in GCA.[53]

With respect to TAK, a higher incidence of Mycobacterium *tuberculosis* infection has been reported in these patients, with molecular mimicry between microbial and human 65 kDa heat shock protein proposed as a triggering immunological event.[54] However, these data suffer from epidemiological confounding and further studies are needed to support this hypothesis.[55] Of note, an Indian study found the frequency of tuberculosis to be 5.6% in patients with TAK, similar to the general population.[29]

Mortality

Data on mortality in GCA are conflicting (**Box 1**). In general, death in GCA is more likely due to accelerated atherosclerosis, rather than direct complications of disease. Indeed, a 2017 meta-analysis demonstrated that the leading causes of death in GCA were cardiovascular disease (excluding deaths related to aortic aneurysm rupture) (39%), cerebrovascular disease (14%), infection (13%), and malignancy (12%), with the remaining 22% accounted for by gastrointestinal, pulmonary and renal deaths, aortic aneurysm-related deaths and deaths not specified.[56] This is perhaps less likely to hold true in those with large vessel complications. Indeed, the mortality in those with ruptured aortic aneurysms as a consequence of GCA (80%) is higher than in those without GCA (65-75%).[57] A recent meta-analysis observed decreasing mortality rates in patients with GCA over the 50-year study period (at a rate of 0.14 per 1,000 people per year).[58] Indeed, it may be that regular monitoring and screening for co-morbidities in patients with GCA has led to comparable mortality rates with that of the general population.

Due to its lower incidence, mortality data for TAK are even less well-defined. Overall, 10-year survival is reported to be ~90%,[59-63] although given the young age at which patients are diagnosed, this may not be that favorable, and several studies suggest 2-3 times higher standardized mortality compared to age-matched healthy controls.[61, 63, 64] Systemic hypertension, major vascular complications, and progressive disease course were associated with increased mortality risk in these studies.

3. MECHANISMS & PATHOPHYSIOLOGY

Loss of arterial wall immune privilege precedes a broad range of aberrant, interlinked immunological responses, involving both the innate and adaptive immune systems, that contribute to the development and progression of disease in LVV. Much of our understanding in this area comes from tissue derived from individuals with GCA. As such, although mechanistic differences exist between GCA and TAK, the two conditions will be largely considered together here.

Loss of tolerance

Under physiological conditions the wall structures of medium and large arteries are shielded from inflammation and autoimmunity by immune privilege. Recent studies in GCA have implicated three mechanisms that contribute to loss of tolerance and disease induction and progression (**Figure 3**):

(1) Loss of anti-inflammatory T regulatory (T_{reg}) cells, which suppress pro-inflammatory T cells in lymph nodes.[65] The age-associated decline of a specialised $CD8^+$ T_{reg} population is mechanistically linked to mis-trafficking of intracellular vesicles. Additionally, recent studies have demonstrated that $CD4^+$ T_{reg} number and function are reduced in active GCA and can be improved with IL-6 blockade.[66, 67]

(2) Deficiencies in the programmed death-1/programmed death ligand-1 (PD-1/PD-L1) inhibitory pathway. This removes a natural break in the adaptive immune system and renders the artery vulnerable to autoimmunity. Both endothelial cells and vascular dendritic cells (DC) are naturally rich in PD-L1 and function as protective shields against activated, injurious PD-1 expressing T cells. In GCA, circulating and vascular DCs lack PD-L1 expression and so activated pro-inflammatory T cells are left unopposed.[68, 69] Blocking the PD-1/PD-L1 pathway results in enhanced vascular inflammation, increased production of T cell cytokines (IFN-γ, IL-17, IL-21), excessive macrophage activation and accelerated intimal hyperplasia.[68, 69] Reports of large vessel inflammation developing in patients with cancer following treatment with

immune checkpoint inhibitors further supports the immunoinhibitory PD-1/PD-L1 pathway as a critical element of the artery's immune privilege.[70]

(3) Leakiness of the endothelial barrier which normally prevents migration of circulating cells into the vessel wall. In LVV, inflammatory cells gain access to the tunica adventitia *via* the adventitial vasa vasorum. In GCA, circulating monocytes produce excess matrix metalloprotease (MMP), digest the subendothelial basal lamina layer, and enable T cells (also independently capable of MMP-2 and MMP-9 production) to infiltrate.[71-74] Adventitial endothelial cells aberrantly express Jagged-1, a ligand for the NOTCH1 receptor, and interact with circulating $CD4^+$ $NOTCH1^+$ T cells,[71, 75] promoting their differentiation into IL-17- and IFN-γ-producing, tissue-invasive effector cells. Finally, immature neutrophils enriched in the blood of patients with GCA are potent producers of reactive oxygen species enabling them to breach the endothelial barrier.[76] Inflammation-dependent neovascularization permits further leucocyte-endothelial cell interaction and inflammation propagation.[77]

Though loss of large vessel immune privilege is also likely to be important in TAK, the precise mechanisms for this remain elusive.[78]

The ageing immune system

Unlike TAK, GCA incidence increases with age, suggesting that the ageing process might influence disease development. The accrual of environmental insults over time results in epigenetic changes with a bias towards inflammation and autoimmunity.[79] In GCA, this manifests in two likely synergistic models:

(1) Reconfiguration of both the innate and adaptive immune systems (immunosenescence), characterized by reduction of naïve T cells and T_{reg} cells, production of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) and reduced cellular responsiveness to inflammatory signals.

(2) Vessel wall remodelling, defined by a reduction in number and function of vascular smooth muscle cells (VSMCs), degeneration of the media, calcium deposition, thickening of the intima

and biochemical modification of matrix proteins; collectively leading to loss of elasticity and pliability.[80]

Unopposed, these create the ideal environment for chronic inflammation to dominate. Though one single infective trigger has not been demonstrated in GCA, there may be a link between persistent or cumulative pathogens and chronic antigenic stimulation leading to loss of antigen independent control by T-cells and activation of vascular DC.[80, 81]

Vascular inflammation

Once immune privilege is lost in LVV, a cascade of pro-inflammatory mediators leads to progressive tissue damage. Vascular DCs are recognized as pathogenic instigators given their position at the adventitia-media interface, their defect in terms of reduced PD-L1 expression, as well as their sensitivity towards Toll-Like Receptor (TLR) activation.[82] Once vascular DCs are stimulated, they migrate and occupy the vessel wall,[83] recruiting and retaining further innate and adaptive immune cells (e.g. T cells); in parallel, infiltrating monocytes differentiate into macrophages and multi-nucleate giant cells. This inflammatory process can persist for years even when, clinically, disease is perceived as quiescent.[84] The concept of persistent smoldering vasculitis that is difficult to detect and quantify is supported by the clinical evolution of disease, with aneurysm formation and progressive arterial occlusion complicating GCA and TAK decades after initial diagnosis.

T cells recruited to and settling in the vessel wall produce a broad spectrum of effector cytokines, which orchestrate immune and vascular cells in tissue destruction and wall remodelling (**Figure 4**). For example, T cells in granulomatous lesions exhibit functional bias towards T helper 1 (Th1) and T helper 17 (Th17) cells.[85, 86] Th1 cells are important sites of IFN-γ production; this drives a smoldering inflammatory process involving macrophage activation and recruitment. Stimulated macrophages amplify inflammation and injury through release of an array of effector molecules, including cytokines (e.g. IL-6, IL-12, IL-23, IL-1), growth factors (e.g. VEGF and platelet derived growth factor (PDGF)), and MMPs (e.g. MMP-

9, MMP-7, MMP-2). Notably, VEGF plays a role in priming adventitial endothelial cells which promotes further T cell influx as well as driving vascular remodelling, intimal thickening, and neo-vascularisation.[71, 87]

Granulocyte macrophage colony stimulating factor (GM-CSF), largely expressed by macrophages and endothelial cells, is an upstream mediator of Th1 and Th17 cells. Inhibition of the GM-CSF receptor pathway in humanized models results in suppression of T cell infiltration and reductions in both intimal thickness and neovascularization suggesting a potent interplay between GM-CSF and the Th1 axis.[88-90] One of the important differences between GCA and TAK is the glucocorticoid responsiveness of T cell mediated inflammation. In GCA, the Th17 axis is sensitive to glucocorticoid treatment, whilst Th1-dependent responses may be more resistant.[91, 92] Conversely, in TAK, Th1-committed T cells appear more glucocorticoid-responsive than Th17 cells.[91, 93]

A consistent finding in the vasculitic infiltrates in LVV is the broad spectrum of T cell effector cytokines, beyond IFN-γ and IL-17, including IL-9, IL-21, and IL-22.[88, 94, 95] It remains unclear whether a cytokine hierarchy exists, what the mechanisms for their induction are, and whether they derive from a common cellular source or from functionally distinct T cell subsets, and whether they have distinguishing pathological roles.

Mechanistic studies have implicated the NOTCH-NOTCH ligand and Janus kinase-signal transducer and activator of transcription proteins (JAK-STAT) pathways and mammalian target of rapamycin (mTOR) signalling as being pathogenically important in both GCA and TAK.[96, 97] Transcriptomic analysis has indicated interferon-induced JAK-STAT signalling, and treatment of human artery-SCID chimera mice with small molecule JAK-STAT inhibitors was highly effective in suppressing vasculitis and the associated cytokine production.[98] mTOR signalling plays a crucial role in polarising T cells towards effector cell status, biasing adaptive immunity towards a pro-inflammatory state. mTOR complex 1 (mTORC1) activation has been shown within the endothelium of the aortic wall as well as within Th1 and Th17 cells derived from inflammatory lesions in both GCA and TAK,[99, 100] identifying mTOR signalling as a universal pathogenic pathway in LVV. Immunophenotyping using DNA methylation profiling has identified a pathogenic role for the calcineurin/nuclear factor of activated T cells (NFAT) pathway, another potential target for future therapeutics.[79]

In addition to differences in glucocorticoid-responsiveness within the Th17 axis, another distinguishing pathological feature between GCA and TAK is the composition of the vessel wall infiltrates. Both share an abundance of highly activated T cells and macrophages organised into granulomata.[83, 87] However, in TAK, aortic wall infiltrates contain a significant population of cytotoxic $CD8^+$ T cells (reflecting the HLA class I association) and natural killer (NK) cells. $CD8^+$ T cells account for ~15% of infiltrating cells in aortic lesions in TAK, and are also seen in higher numbers in the circulation.[45, 101] However, recent studies have demonstrated elevated circulating cytotoxic $CD8^+$ T cells in patients with GCA compared to controls. $CD8^+$ T cells have also been noted within diseased temporal artery tissue, a finding which associates with a more aggressive disease phenotype.[102] $CD16^+$ NK cells represent ~20% of all immune cells in TAK lesions,[45] suggesting a pathogenic role for cytotoxicity in mediating vessel wall injury. It should be noted, however, that histological examination in TAK most often occurs years after disease onset, as opposed to early examination of TAB in GCA. This difference may account for some of the discrepancies seen.

Vascular injury and remodelling

Persistent intramural inflammation leads to structural change within the diseased vessel wall. Neovascularization not only sustains the resident vascular inflammation but allows further recruitment of pro-inflammatory leucocytes.[77] Ultimately, a maladaptive vascular repair process is initiated whereby stromal cells (primarily endothelial cells, VSMCs and fibroblasts) expand and differentiate to drive laminar necrosis, intimal hyperplasia and fibrosis.[103] VSMCs are thought to be key players in this process, undergoing phenotypic modulation by resident macrophages and Th1 cells, including PDGF and endothelin-1 signalling.[104, 105] Activated VSMCs proliferate and invade the intima where they deposit extracellular matrix proteins. The resultant intimal expansion leads to eventual luminal stenosis and ischemic complications.

Recent work has highlighted the role of mast cells in the pathogenesis of TAK lesions. In a series of *in vitro* and *in vivo* experiments using serum and aortic tissue from both healthy controls and patients with TAK, mast cells were responsible for increased vessel wall permeability, neovascularization, and fibrosis; these cells represent a potential therapeutic target.[106]

Extravascular systemic inflammation

Emerging data suggest that vascular inflammation in LVV is often combined with an extravascular a systemic inflammatory component, and that these may operate autonomously with regards to disease mechanisms, clinical phenotypes, and therapeutic responses. This systemic inflammatory response in LVV is characterized by a florid acute phase reaction, manifesting as hemopoietic (anemia and thrombocytosis) and liver function abnormalities, and significant elevations in erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). The clinical phenotype is one of fever, malaise and myalgia. The cytokine clusters of IL-6, IL-8, IL-12p70, monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-1β (MIP-1β), eotaxin and pentraxin-3 (PTX-3) act upstream and stimulate hepatocytes to produce acute phase proteins.[107] The triggers for unleashing this cytokine cluster remain unknown, but IL-6 and PTX-3 represent potentially useful upstream targets for suppression of systemic inflammatory disease. Although the ease of measuring ESR and CRP allows swift assessment of this extravascular component, they cannot measure the burden of inflammation within the vessel wall.

B cells in LVV

Chronic tissue inflammation is associated with the formation of tertiary lymphoid organs, exemplified by the accumulation of lymphoid aggregates in the perivascular tissue of atherosclerotic arteries and the aneurysmal aortic wall.[108, 109] B cell clusters have been reported in the adventitial layer of TAK-affected aorta, whilst organised B-cell infiltrates have also been confirmed within the aneurysmal aortic wall of patients with LV-GCA.[109, 110] Varying in complexity, these structures are rich in T and B cells and may have pro- and anti-inflammatory functions. Systemic inflammation in GCA is associated with changes in circulating B cell numbers and their ability to produce IL-6.[111] A potential pathogenic role of autoantibodies has been suggested by the identification of endothelial cell autoantigens in TAK.[112] A potential role for B cells in TAK pathogenesis is also supported by the findings of a recent large GWAS study.[49] Additionally, recent work in TAK has highlighted a novel follicular helper T cell signature which may promote B cell activation and function.[113]

4. DIAGNOSIS, SCREENING & PREVENTION

No validated diagnostic criteria exist for GCA or TAK. Historically, a diagnosis of GCA was based upon a constellation of symptoms, ideally with histologic confirmation of vasculitis. Incorporation of vascular imaging into diagnostic assessment may complement or even supplant tissue diagnosis in C-GCA and is generally considered mandatory to diagnose LV-GCA and TAK. In 2018, the European Alliance of Associations for Rheumatology (EULAR – previously European League Against Rheumatism) proposed management recommendations in LVV which advocated for multidisciplinary diagnostic evaluation by specialists.[8] Given the potential for irreversible vision loss associated with diagnostic delay, 'fast-track' referral pathways have been developed for patients with GCA and demonstrate improved clinical outcomes and reduced healthcare costs.[114]

Common presenting features

Clinical features of LVV can be due to vascular inflammation, ischemia, or both (**Table 2**). In some cases, a diagnosis of LVV is suspected in an asymptomatic patient based on findings from the vascular examination or imaging studies.[34] Vision disturbance requires urgent ophthalmological assessment to reduce rates of permanent vision loss.[115] Treatment initiation at time of referral is recommended if the diagnosis of LVV is strongly suspected and always when sight is threatened.[114] Initial investigations are influenced by presenting features, physician preference and availability of imaging modalities (**Figure 5**).

Initial investigations

As the presenting features of LVV may be non-specific, initial investigations (**Table 3**) should aim to exclude mimics such as infection or malignancy (**Table 1**). Raised inflammatory markers (such as ESR or CRP) are observed in most patients with active disease, although may be more modestly elevated in TAK compared with GCA. [34, 116, 117]

Imaging-based *versus* histological diagnosis

TAB is a useful investigation for suspected C-GCA or LV-GCA with cranial involvement. Previously considered the gold-standard for diagnosis, advances in the reliability of vascular imaging techniques have meant that reliance on TAB in some centers has declined.[114] Indeed, several high-quality studies have demonstrated equivalent diagnostic accuracy between imaging and TAB.[114] Additionally, at least in the case of ultrasound, imaging is more cost-effective and less invasive.[118] When considering which investigation might best suit the individual, the clinical pre-test probability of GCA should be considered.[114, 119] Ultrasound alone may be sufficient to both exclude GCA in cases of low-pre-test probability, and to confirm GCA in cases of high pre-test probability. In those with an uncertain pre-test probability, or in whom ultrasound has failed to confirm the diagnosis, TAB is recommended. This slight shift in focus has been accelerated by the increased recognition of large vessel involvement in GCA, something that TAB fails to identify.[6] Nevertheless, TAB is still an important consideration in the diagnostic pathway of C-GCA. In many parts of the world, particularly North America, TAB remains the recommended first line investigation in suspected C-GCA.[120, 121] Despite this, we favor the diagnostic approach outlined above and adopted by both EULAR and the British Society for Rheumatology, provided sufficient expertise with using ultrasound exist.[114, 119] TAB has no role in TAK, where temporal artery involvement is unusual. Histological diagnosis in TAK is only possible in exceptional circumstances or in the post-operative setting, such as following aortic valve replacement.

Choice of initial imaging modality

Multiple imaging modalities are available to assess extent and severity of LVV, including ultrasound, magnetic resonance imaging (MRI), computed tomography (CT) and ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET). Each modality has advantages and disadvantages, and choice of imaging is typically guided by clinical scenario and local expertise. It is recommended that imaging of the aorta and major branches is considered in all patients, even in those with a primarily cranial presentation, as presence of great vessel involvement may influence treatment strategy and prognosis (**Figure 5**). It should be noted that the diagnostic accuracy of the imaging modalities described declines quickly following treatment with glucocorticoids (GC) and imaging is best performed within one week of starting therapy.[118, 119, 121] Accordingly, the use of imaging for disease monitoring presents many challenges and is considered separately (**Box 2**).

Ultrasound

In suspected C-GCA, ultrasound is considered by many to be the initial investigation of choice. Demonstration of features including a thickened vessel wall (halo sign) and one which remains visible following compression of the lumen (compression sign) provides a diagnostic sensitivity of 77% and specificity of 96%.[122] While ultrasound is useful to assess the temporal and axillary arteries, two common sites of inflammation in GCA, its use to detect pathology in the aorta is limited. Assessment of the carotid and subclavian vessels by ultrasound may have utility in TAK.[123] Although ultrasound is safe, inexpensive, and widely available, differences in performance and data interpretation can lead to reduced inter-reporter reliability. The TABUL (Role of Ultrasound Compared to Biopsy of Temporal Arteries in the Diagnosis and Treatment of GCA) study, the largest study of its kind, recruited 381 patients with a suspected new diagnosis of GCA to undergo both ultrasound (axillary and temporal) and TAB within 10 days of starting treatment. Ultrasound had superior sensitivity over TAB (54% *vs.* 39%) but inferior specificity (81% *vs.* 100%) compared to clinical diagnosis of GCA as the reference standard.[118] The lower-than-expected diagnostic accuracy of ultrasound in this study may relate to the inexperience of some operators. Indeed, sensitivity improved by 17% once operators had completed at least 10 scans. It must be noted, however, that the diagnostic sensitivity of TAB is also operator dependent, influenced both by specimen adequacy and expertise of the reporting pathologist.[118] Where diagnostic uncertainty exists, there may be a role for both ultrasound and TAB.[114, 118]

MRI

Whilst prone to less inter-operator variability than ultrasound, MRI is more expensive and less widely available. MRI provides a thorough assessment of the vessel wall and, when combined with MR angiography (MRA), can accurately identify luminal abnormalities. It requires no radiation exposure and although few data support its accuracy, MRI/MRA is considered first-line imaging for suspected TAK as these patients are generally younger and may require interval scans.[124] Although MRI/MRA may be appropriate first-line imaging for suspected LV-GCA there is little to support its superiority over CT or PET. When ultrasound is unavailable in suspected C-GCA, high-resolution MRI of the cranial arteries provides comparable diagnostic accuracy.[122]

CT angiography

CT angiography (CTA) is quicker and more widely available than MRI, with a sensitivity of 73% and specificity of 78% for diagnosing LV-GCA.[125] EULAR do not recommend its use for cranial disease and, although an option for suspected large vessel disease, the ability of CTA to identify vessel wall edema and inflammation is probably inferior to MRI.[119] Obligatory radiation exposure makes CTA less favorable for younger patients with TAK. CT may be a useful initial investigation in situations where LVV is one of several possible diagnoses. In such cases (for example, pyrexia of unknown origin) CT (either alone or combined with PET) may be the preferred imaging modality.

PET

PET imaging, mostly performed with fluorodeoxyglucose (FDG) radiotracer, provides a functional map of large vessel inflammation. Contiguous, high-grade vascular FDG uptake affecting multiple arterial territories is typical of active LVV.[126] Alternative causes of vascular FDG uptake, primarily atherosclerosis, can introduce diagnostic uncertainty, and several quantification methods have been proposed to distinguish LVV from atheroma and other mimics.[126] Areas of maximal FDG uptake are typically referenced to ‘background’ uptake values (such as liver or venous bloodpool) with cumulative arterial territory scores such as the

PET Vasculitis Activity Score (PETVAS) used to reflect disease burden.[127] A 2015 meta-analysis of 11 studies (4 in GCA (57 patients) and 7 in TAK (191 patients)) evaluated the diagnostic efficacy of PET in LVV and demonstrated pooled sensitivities and specificities of 90% and 98% for GCA, and 87% and 73% for TAK.[128] Recent evidence suggests that PET may also be useful to detect vascular pathology in the cranial arteries in addition to the aorta and branch vessels.[129, 130] Additionally, baseline PET metrics may have a role in predicting disease course.[131]

There are, however, clear drawbacks with PET including access, cost, and long procedure times. Additionally, vascular FDG uptake is attenuated rapidly following treatment initiation. A study by Nielson *et al* examined the diagnostic accuracy of PET following the introduction of high dose prednisone in 24 patients with active LVV. After 3 days of treatment FDG signal was reduced but remained diagnostic in 100%; by 10 days this had fallen to 36%.[132] PET also requires a second imaging modality to map the low-definition functional image. Traditionally this has been CT, allowing impressive structural and functional imaging data to be collected simultaneously, albeit with significant radiation exposure.

More recently, hybrid scanners combining PET with MRI (PET/MR) have demonstrated promising results produced with a fraction of the radiation exposure (**Figure 6**).[133, 134] Further studies will determine if hybrid PET/MR is a useful diagnostic tool in LVV. Additionally, advances in PET radiotracers may allow us to discriminate active vascular inflammation from other pathologies including atherosclerosis.[135] Radioligands with specific affinity for activated macrophages such as ^{11}C-(R)-PK11195 have shown promise in small studies demonstrating ability to track inflammation and differentiate active LVV from inactive disease.[136] Whether combined with CT or MRI, PET may be of particular value in cases of diagnostic uncertainty, for example, to exclude occult malignancy.

Disease relapse

Risk of relapse in LVV is high and remains elevated for years after diagnosis. EULAR guidelines define ‘major relapse’ as recurrence of clinically active disease alongside features of ischemia or radiologically confirmed aortic inflammation, and ‘minor relapse’ as recurrence of disease not fulfilling these criteria.[8]

Relapse risk in GCA has been reported as ~30-75% over the disease course but particularly within the first 2 years following diagnosis.[137, 138] A retrospective US cohort of 286 patients with biopsy-proven GCA reported a relapse rate of 74% over a median of 5.1 years with female patients and those with pre-existing hypertension and diabetes at particular risk.[139] Involvement of the aorta and major branches also appears to confer an increased relapse risk.[16] For patients with TAK, disease relapse rates are ~20% at 1 year and ~50% at 10 years.[140] Male sex, elevated CRP and carotidynia at presentation are associated with higher relapse risk.[140] Accurate disease monitoring is key to the early recognition and treatment of relapse. Such tools are important for tracking persisting, smoldering inflammation that has been demonstrated in pre-clinical and clinical studies, but which does not meet the criteria for relapse and may be clinically silent.[83, 84]

Disease monitoring

Disease monitoring is crucial to accurately match treatment intensity with disease activity. Several disease activity assessment tools have been proposed however none has yet been widely accepted for use either clinically or for research purposes. Consequently, escalation and de-escalation of treatment is based upon a combination of clinical assessment, laboratory investigations, and imaging.

Clinical assessment

Accurate monitoring of disease activity by clinical assessment alone can be challenging in the later phases of LVV. Symptoms such as fatigue and pain may reflect active inflammation or be consequences of established vascular disease, treatment, anxiety, or a separate disease process entirely. Similarly, arm claudication may be modifiable with treatment if due to active vessel inflammation or may be chronic and treatment-refractory if related to vascular damage. Rigorous assessment at presentation, and care continuity within the same clinical team, are important to recognize subsequent disease progression expeditiously.

Laboratory markers

CRP and ESR are often used for disease monitoring but may not correlate with clinical or vascular disease activity, particularly once treatment has started. In a study of biopsy-proven GCA, 24/25 patients had a normal ESR by day 28 of GC treatment.[141] Fifteen patients relapsed with a total of 31 relapses; of these, 42% had a normal ESR at time of relapse. In this study, IL-6 was a more sensitive marker of active disease, and in those achieving complete clinical remission, IL-6 remained high in 67% whereas ESR was high in only 12.5%, supporting grumbling inflammation. In a recent study of 112 patients with LVV (56 with GCA, 56 with TAK), the authors found only a modest correlation between CRP (but not ESR) and outcome measures, including physician and patient reported outcomes, and PET imaging.[142]

Novel biomarkers of LVV disease activity with better performance characteristics compared to clinical and imaging-based based reference standards are urgently needed. Advances in our understanding of disease pathogenesis have identified potential candidates. In 2003, Matsuyama and colleagues demonstrated a correlation between TAK disease activity and MMP-3 and -9, two proteinases involved in disease pathogenesis.[143] PTX-3 is produced at sites of inflammation and serum levels correlate with vascular inflammation in vasculitis.[144, 145] Dagna and colleagues found that circulating PTX-3 was higher in patients with clinically active TAK than in inactive disease, healthy controls and acute infection. PTX-3 also distinguished active from inactive disease better than CRP or ESR.[146] Elevated PTX-3 levels also correlate with active GCA, particularly in those with recent optic nerve ischemia.[107] Although several other candidate biomarkers remain under investigation – including serum amyloid A, osteopontin, aminoterminal pro-B-type natriuretic peptide (NT-proBNP) and calprotectin –

none has been incorporated into widespread clinical use. Potential novel biomarkers may have a role beyond diagnosis and disease monitoring, including prognostication and assessment of vascular and end-organ damage, though further work is required.[147]

Imaging

The ideal imaging modality for disease monitoring in LVV should be safe, widely available, cost-effective, and able to distinguish persisting vascular inflammation from vascular remodeling and alternative conditions – most notably atherosclerosis. There is no current consensus on how frequently imaging should be performed in this setting, and decisions should be made on an individual basis. The advantages and disadvantages of different imaging modalities for LVV disease monitoring are highlighted in **Box 2**. This is an area of unmet need as highlighted by the 2018 EULAR LVV research agenda.[119]

Disease activity assessment tools

The importance of developing a robust disease severity scoring system has been recognized by the LVV research community. Although several assessment tools exist these are mostly used as endpoints in clinical trials rather than for clinical purposes (**Table 4**). Unfortunately, there is no well-defined reference standard of disease activity against which new tools may be compared, presenting a major challenge for clinical trialists.

Disease complications

Unchecked vascular inflammation may lead to a range of disease complications in LVV. In the short-term, vision loss is the most feared complication of GCA and occurs in ~15-20% of patients.[148] Anterior ischemic optic neuropathy (AION) is the commonest pathology and may be halted by prompt initiation of GC. While symptoms such as diplopia and blurred vision may improve with treatment, complete monocular vision loss is unlikely to recover, and the goal of therapy here is to prevent bilateral vision loss. Encouragingly, vision loss is far less common during disease relapse compared with initial presentation, an important consideration during treatment reduction or withdrawal.[137]

Large vessel involvement in GCA associates with a higher mortality, a potentially greater risk of relapse, and higher cumulative GC exposure.[16, 149] A 2019 retrospective analysis compared 183 patients with LVV aged 50-60 with 183 patients aged >60 years. Younger patients had a higher incidence of aortic and peripheral vascular involvement, and required more treatment than older patients.[150] Similarly, in a cohort of 332 GCA patients, 14% of those with large vessel involvement at diagnosis had developed aortic aneurysms within ~4 years, compared with 5% of those with cranial GCA at outset.[16] In a large UK study, the risk of aortic aneurysm formation in GCA was 2-fold higher than in matched controls.[151] Due in large part to a continued reliance on GC, complications of treatment remain a significant cause of morbidity in GCA with adverse effects occurring in >80%.[152]

TAK is associated with frequent large vessel complications, which are commoner than in GCA.[153] Complications, in order of frequency, include new arterial occlusion (42%), stroke or transient ischemic attack (20%), new or worsening aneurysm (11%), end-stage kidney disease (10%), myocardial infarction (6%), heart failure (6%) and aortic regurgitation (5%).[140] These are more likely in those with progressive disease, thoracic aorta involvement and in those with retinopathy.[140]

5. MANAGEMENT

There are two stages in the pharmacological treatment of LVV. Induction of disease remission, which aims to suppress initial vascular inflammation and typically requires high doses of GC, and remission-maintenance, aimed at preventing disease flares (**Figure 8**). The evidence-base for treatment is more robust for GCA, whereas the treatment of TAK is largely based on expert opinion.

Remission-induction

Although never subjected to RCT evaluation, GC are the mainstay of treatment for remission-induction in LVV. GC induce rapid symptom relief and reduce the risk of vision loss in GCA. The optimal initial dose of GC, and its route of administration, have not been investigated but is usually 40-60 mg of oral prednisone (or equivalent) per day, as recommended by EULAR guidelines for both GCA and TAK.[8] To attempt more rapid and broader effect, patients with GCA-related sight-threatening symptoms may be given pulsed intravenous methylprednisolone. However, there is little evidence to support this approach, and it may increase the risk of GC-related complications, as seen in other vasculitides.[154] In select patients with TAK, for example those without flow-threatening lesions, lower initial prednisone doses may be considered (25-30 mg/day). TAK may also present without clinical, serological or imaging-based evidence of disease activity (*i.e.* 'burnt-out' disease). In such patients, the benefit of treatment with GC or other disease-modifying therapies is unknown.

An open-label study of 18 patients with GCA tested the ability of the IL-6 receptor antagonist, tocilizumab, to induce disease remission following three intravenous pulses of methylprednisolone.[155] 78% of patients achieved remission within 24 weeks and 72% were relapse-free at week 52. Five out of 18 (28%) stopped treatment due to non-response or tocilizumab-related adverse events. Although tocilizumab monotherapy may induce disease-remission following brief GC exposure, remission-induction is slow and persisting disease activity may lead to ongoing symptoms or irreversible complications such as AION (as developed by one patient during the study). Thus, tocilizumab monotherapy cannot currently be recommended for remission-induction.

Remission-maintenance

Disease remission in LVV is defined as the absence of any clinical features attributable to active disease, normalization of laboratory parameters, and a halt in progression of vascular imaging abnormalities.[8]

Glucocorticoids

Once initial disease control is achieved, GC are tapered to reduce side effects. Tapering is usually initiated after 2-4 weeks. The optimal pace of GC tapering has not been established and probably varies between patients. In general, to achieve a compromise between relapse risk and GC-related side effects, which are common,[156] particularly in elderly patients,[152] it is recommended that tapering should aim to achieve 15-20 mg of prednisone (or equivalent) per day after 2-3 months and to ≤5 mg/day after 1 year. GC tapering is usually slower for TAK, and a target dose of ≤10 mg/day should be achieved at 1 year.[157]

However, LVV relapses in 34-75% of patients when GC are reduced,[158] usually below prednisone 20 mg/day.[138] In general, GC minimization results in higher relapse rates[159] and clinical trials have shown that only ~20% of patients with GCA in placebo arms maintain sustained remission at 1 year after an aggressive GC taper and early discontinuation at 22-26 weeks.[160, 161] Most patients require longer treatment periods. In a recent RCT, two different tapering regimens were compared in the placebo arm with discontinuation at 26 or 52 weeks. Relapses occurred in 68% and 49%, respectively.[161] With respect to TAK, a rapid GC taper results in relapses in ~60-80% of patients at the end of follow-up.[162, 163]

GC monotherapy may be considered as an option for maintaining disease-remission in GCA as ~40% of patients can reach the target of ≤5 mg/day at one year, a dose considered safe.[164] When used in this way, GC treatment should be continued for a minimum of 2 years.[8]

Conversely, GC monotherapy is less effective in TAK.[140, 162, 163] Since TAK evolves as a more chronic, grumbling, and relapsing disease than GCA, the addition of disease-modifying therapy early is recommended.[8]

Disease-modifying or glucocorticoid-sparing treatments

Current guidelines recommend the use of a disease-modifying agent in patients with GCA who have relapsing or refractory disease, or in those with an increased risk of GC-related side effects. Increasingly, physicians are opting for these treatments earlier in the GCA treatment pathway, with some adopting initial combination therapy as standard practice in patients with large vessel involvement.[121] In TAK, the combination of GC and a GC-sparing agent is considered first-line due to the potential for higher relapse rates and disease progression in those treated with GC alone.[8, 29, 165] In addition to traditional broad-spectrum GC-sparing agents, novel biologic agents are now available for use in LVV.

Broad-spectrum immunosuppressive agents

Methotrexate (MTX) has been tested in three randomized, double blind, placebo-controlled trials in patients with newly diagnosed GCA.[166-168] Although results of these were unconvincing, an individual patient-level meta-analysis of all three studies demonstrated a reduced risk of disease relapse and reduced cumulative GC exposure in those treated with MTX compared with GC alone;[169] a second meta-analysis did not replicate this finding.[170] MTX doses used in these trials were generally low (7.5-15 mg/week) and higher doses have not been formally tested but are used in clinical practice. Observational, real-life data, also support an effect of MTX on reducing GCA disease relapses and sparing GC.[171]

The GC-sparing activity of several other immunosuppressive agents has been reported in low-quality studies (mostly retrospective or case series) including leflunomide,[172] mycophenolate,[173] dapsone[174] and cyclophosphamide.[175, 176] In a small, randomized trial, cyclosporin did not show significant GC-sparing activity, and azathioprine showed a GC-sparing effect in a mixed population of patients with GCA and PMR.[175]

Given the frequently relapsing course of TAK, it is often a more difficult disease to control. No RCT of broad-spectrum immunosuppressive agents has been performed in these patients. MTX, azathioprine, mycophenolate and leflunomide have all been reported as potentially useful.[157, 177] Unless other therapies fail, cyclophosphamide is not generally recommended in TAK because of its adverse effects on fertility. Physician expertise, patient preferences, comorbidity and side effects usually dictate choice of treatment.

Targeted biologic therapies

Improved understanding of specific disease pathways involved in the pathogenesis of LVV has paved the way for targeted biologic therapies (**Figure 4**), some of which have demonstrated efficacy in phase 2 and phase 3 clinical trials, and others which are currently under investigation.

GCA

Tocilizumab

After a promising phase 2 trial,[178] the efficacy of blocking the IL-6 receptor with the humanized monoclonal antibody, tocilizumab, has been demonstrated in the phase 3 GiACTA trial, which included both newly diagnosed and relapsing patients with GCA.[161] Compared with placebo, treatment with tocilizumab resulted in a significantly increased proportion of patients in sustained remission at week 52, a longer time to disease flare, decreased cumulative GC doses, and improvements in quality of life.[161, 179] Subcutaneous administration of 162 mg weekly achieved better disease control than 162 mg every other week, particularly in relapsing/refractory cases.[161]

A number of observational clinical studies, which have included a higher proportion of relapsing patients with GCA as compared with clinical trials, have used tocilizumab as add-on therapy.[180] These studies show fewer disease flares than seen in the GiACTA trial, possibly because low-dose GC or concomitant immunosuppressive treatments were not discontinued in a substantial proportion of patients.[180, 181] One study also showed more infections in tocilizumab-treated patients.[182]

Tocilizumab has been a major therapeutic advance and is now licensed for the treatment of GCA in both the US and Europe. However, >40% of patients are unable to maintain disease-remission despite adherence to recommended GC tapering, and extended follow-up data show that only 40% of initial responders maintain treatment-free disease-remission after 3 years. This is supported by observational data.[181, 183] Thus, tocilizumab may need to be continued for longer periods of time and other options are needed.[184]

There also remain questions around biomarkers of disease activity in patients receiving tocilizumab, given that the routinely measured acute phase reactants are abrogated by tocilizumab.[185] One worry is the potential for undetected, grumbling large vessel inflammation with tocilizumab use and GC minimization. Case reports have demonstrated histologically active vasculitis despite clinically quiescent disease and suppressed acute phase reactants in those receiving tocilizumab.[186, 187] Imaging biomarkers may be useful here.[188-190] Until more long-term follow-up data are available, many health care providers reserve tocilizumab for patients with, or at risk of, GC-related side effects or patients with relapsing disease.

Mavrilimumab

Mavrilimumab is a fully humanized monoclonal antibody targeting the GM-CSF receptor-α. GM-CSF and its receptor are expressed in GCA and preliminary results in functional models suggest a role of GM-CSF in key pathogenic aspects of GCA including dendritic cell activation, T-cell differentiation and pro-inflammatory macrophage activation.[191] A recent phase 2 study demonstrated that mavrilimumab alongside a 26-week prednisone taper was superior to placebo plus 26-week prednisone taper for time to disease flare. Sustained disease remission at week 26 was achieved in 83% of mavrilimumab recipients and in 50% of those receiving placebo.[192] It is noteworthy that acute phase reactants retain their clinical value under mavrilimumab treatment. Thus, mavrilimumab has promise as a novel therapeutic option for patients with GCA, although efficacy and safety need to be confirmed in larger trials.

Abatacept

Abatacept is a recombinant CTLA-Ig molecule that inhibits CD28-mediated T-cell activation. A phase 2 RCT recruited patients with active disease and, after an initial 3-month combination treatment with GC and abatacept, patients in remission were randomized to continue abatacept or receive placebo in addition to standardised GC taper with discontinuation at 28 weeks. Relapse-free survival at 12 months was slightly higher in the abatacept arm (48% *versus* 31%).[193] The efficacy of abatacept is currently being explored in a phase 3 investigator-sponsored RCT (NCT04474847).

TNF inhibitors

TNF-α is strongly expressed in GCA lesions and along with IL-6 is elevated in serum from patients with a strong acute phase response and remains elevated in relapsing patients.[194, 195] However, although TNF inhibitors, including infliximab, etanercept and adalimumab, have been subjected to RCT evaluation in newly diagnosed patients with GCA, they have failed to demonstrate significant benefits.[160, 196, 197] These data underline that a biomarker of disease activity may not be necessarily a therapeutic target. As such, TNF inhibitors are not recommended for patients with GCA.[8]

Ongoing phase 2 and phase 3 trials

Novel models using murine engraftment of human arterial tissue followed by induction of LVV-like inflammation now allow assessment of therapeutic strategies specific to large vessels.[198] Work using such models has suggested a potential role for JAK inhibitors in GCA.[98] The JAK1 inhibitor, upadacitinib, is now being evaluated for the treatment of GCA in a multi-center, randomized, double-blinded, placebo-controlled trial (NCT03725202). There are several other ongoing phase 2 and phase 3 trials in patients with GCA, the results of which are eagerly awaited (**Box 3**).

TAK

As TAK is less common than GCA and assessment of disease activity may be more difficult, there are fewer clinical trials in these patients.

Tocilizumab

The efficacy of tocilizumab was tested in a RCT including 36 patients with relapsing TAK.[162] Although the primary endpoint (time to relapse) did not reach statistical significance between treatment arms, there was a favourable trend and no safety concerns were raised. Extended follow-up of this trial,[199] observational studies and case series support a sustained benefit of tocilizumab in TAK.[200-202]

TNF inhibitors

Again, although no RCT data support their efficacy, TNF inhibitors are used in clinical practice for those with refractory disease, and increasingly in some centres as first-line GC-sparing therapy.[157, 203] Retrospective analyses suggest better outcomes in patients with TAK receiving biologic therapies than broad-spectrum immunosuppressive agents.[200-203] A multicentre analysis led by the French Takayasu Network examined outcomes in 209 patients with TAK treated with either tocilizumab or TNF inhibitors. They found no difference in rates of complete remission at 6 months (~70%) and prevention of relapse.[204]

Abatacept

Abatacept was tested in a phase 2 RCT and, in contrast to GCA, failed to demonstrate any benefit over placebo in patients with TAK.[163]

Other agents

Case series and uncontrolled small studies have reported satisfactory responses to different agents including ustekinumab,[205, 206] rituximab,[207] and JAK inhibitors.[208] Several other agents remain under investigation (**Box 3**).

Revascularization and aneurysm repair

Revascularization procedures play an important role in the management of patients with TAK. They may be necessary when vascular lesions are organ-threatening (e.g. critical carotid or vertebral stenoses), causing complications (e.g. uncontrolled renovascular hypertension) or if they persist despite optimal pharmacological treatment.[8, 157] Percutaneous angioplasty and open surgical approaches are both possible, and outcomes are broadly similar.[209] Simple balloon angioplasty may be preferable to stenting as in-stent stenosis seems to be more frequent than in atherosclerotic lesions, though experience comes mostly from observational studies.[210, 211] The use of drug-coated balloon renal artery angioplasty is being evaluated in a RCT (NCT04366596). Immunomodulatory therapy should be optimised prior to any attempted revascularization and procedures should ideally be performed in patients in established disease-remission.[212] Reduced patency, re-stenosis and complications are more frequent when manipulating arteries with active disease.[212]

Revascularization is infrequently needed in GCA, a disease with a lower incidence of stenosis than TAK. Its use for limb artery stenoses has been reported.[213, 214] Percutaneous angioplasty should be considered in patients with stroke or transient ischemic attacks due to proximal carotid or vertebral stenoses.[215, 216] Aortic aneurysm repair may be needed in both TAK and GCA and requires joint long-term management with cardiothoracic surgeons.[8, 157]

Cardiovascular disease risk

Chronic smoldering inflammation and prolonged GC exposure contribute to an increased risk of cardiovascular disease in LVV. This is due, in part, to the development of risk factors such as hypertension, diabetes and hypercholesterolemia which should be managed according to standard guidelines. Population studies have demonstrated an increased risk of myocardial infarction, stroke and atherosclerotic peripheral vascular disease in GCA *versus* healthy controls.[217] A Canadian retrospective cohort study compared 1,141 patients with GCA and 200,000 healthy controls aged >65 years without pre-existing cardiovascular disease. Adjusted hazard ratio (HR) for the composite endpoint of coronary artery disease, stroke, peripheral vascular disease, aortic aneurysm or dissection was 2.1 in GCA *versus* controls.[218] These findings were replicated in a smaller but more carefully matched study which suggested a HR of 1.8 for myocardial infarction and 2.0 for stroke in GCA.[219] In contrast, a UK data linkage study examined cardiovascular outcomes in >10,000 patients with either PMR, GCA or both, and >100,000 matched controls.[220] There was no difference in incident cardiovascular disease, although follow-up was limited to ~3 years.

Cardiovascular disease may be more readily observed in younger patients with TAK due to their longer life expectancy,[221, 222] although supporting data are more limited than in GCA. Arterial stiffness, an independent predictor of all-cause and cardiovascular mortality, is increased in patients with TAK.[223, 224] Another study found an increased burden of carotid atherosclerotic plaque in 30 patients with TAK compared with 50 matched healthy controls.[225] Plaque burden was similar to a third group of patients with systemic lupus erythematosus.

Although antiplatelet agents have been used in some centers, current evidence does not support their routine use in GCA.[226] Prophylactic aspirin prescription is more common in TAK and is supported by a small, retrospective Brazilian study which reported a reduction in ischemic events.[227] It must be noted, however, that >90% of patients included had existing cardiovascular disease. Accordingly, anti-platelet agents should be considered on an individualized basis in both GCA and TAK (for example, in those with coronary arteritis, a history of amaurosis, or symptomatic supra-aortic disease). As novel treatments continue to improve outcomes, cardiovascular risk reduction will become increasingly important, particularly in younger patients.

6. QUALITY OF LIFE

Several studies have demonstrated impaired quality of life as a consequence of LVV[228-230] comparable to that in rheumatoid arthritis.[229] This may be due to the impact of active disease, disease complications, or the side-effects of immunosuppressive therapies. It is unique to each affected patient (**Box 4 – patient perspective**). Impaired quality of life may be less apparent in C-GCA[231] where concerns about vision loss dominate.[232] In those with large vessel involvement, the adverse effects on quality of life appear consistent between GCA and TAK despite the age difference between cohorts.[230]

Qualitative studies have attempted to determine which specific patient-reported outcomes are most influenced by LVV.[232, 233] A study of patients with TAK in both the US and Turkey suggested that almost all areas of day-to-day life were affected including employment, family life, finance and self-care.[233] During periods of active disease, fatigue and pain were the dominant factors reducing quality of life, whereas during remission, the emotional burden of disease was more significant. Functional impairment in this young patient group should not be underestimated. In a US cohort of 30 patients with TAK with a median age of 27 years at diagnosis, >60% had difficulty with routine activities of daily living, and 23% were unable to work due to disability.[153]

Recognizing that standardized health questionnaires may not accurately capture the complexities of LVV disease impact, efforts are ongoing to construct disease-specific patient-reported outcome measures in both GCA and TAK. A recent Delphi exercise conducted by the OMERACT (Outcome Measures in Rheumatology) group evaluated which disease-related items were of most value to both clinicians and patients when determining disease activity in LVV with the aim of creating a multi-dimensional tool for use in future studies.[234] The outcomes identified as most important to patients were fatigue, pain and the emotional impact of disease.

Due to the absence of any one single reliable measure of disease activity in LVV, assessments of quality of life and other patient-reported outcomes have been evaluated as potential disease biomarkers for use both clinically and in trials. In a US-based prospective cohort study of 112 participants (56 with GCA, 56 with TAK), patient global assessment of disease activity scores independently associated with clinically active disease.[230] This study demonstrated a complex relationship between other patient-reported outcomes and clinical (laboratory, imaging, and physician-based) outcomes. Accordingly, composite measures of disease activity, combining clinical- and patient-reported outcomes, including quality of life assessment, may provide a more accurate reflection of disease activity.

Understanding that attainment of disease remission is only one aspect of a patient's disease burden may be an important step towards improving the patient journey in the longer term. Interestingly, the GiACTA trial reported that attainment of remission by pharmacological therapy only modestly impacted quality of life indices.[161] Non-pharmacological interventions including exercise and psychological therapy may have a role, as has been demonstrated in other rheumatological conditions,[235] as could supporting access to employment where possible.[236] Future work should continue to focus on what matters most to patients in order to provide sustained improvements in quality of life.

7. OUTLOOK

The last decade has seen significant advances in our understanding and ability to manage LVV. However, morbidity remains high; in GCA vision loss is too frequent and in TAK premature mortality is a continued concern.[237] Likewise, side effects from immunosuppressive therapy, particularly GC, represent an unresolved dilemma. Key future challenges and aspirations include the need for improved understanding of pathogenesis, earlier diagnosis and more targeted therapeutic approaches underpinned by clinical trial data. The next decade, therefore, offers huge opportunity.

Molecular and cellular studies of the arterial wall in LVV are beginning to point the way to improved understanding of disease pathogenesis. Recognition of the differences between GCA and TAK, with definition of both shared and disease-specific pathogenic mechanisms will be critical.[81] Access to tissue is a significant challenge. TAB have accelerated progress in GCA, including identification of the importance of NOTCH ligand Jagged1.[238] The ageing immune system is pertinent to GCA, with defects in both the PD-1/PD-LI immunoinhibitory checkpoint[69] and immunosuppressive function of $CD8^+$ T regs reported.[239] Similarly, further defining the relative importance of lesional $CD4^+$ and $CD8^+$ T cells in LVV,[101] as well as investigation of persistent tissue-resident T cells, will help direct novel treatment approaches.[97, 98]

The role of additional cell types in the various stages of LVV and their potential as therapeutic targets merits further study. These include NK cells[44] and suppressor neutrophils.[240] The role of both B cells and the vascular endothelium in the pathogenesis of GCA and TAK has also received renewed attention. Antibodies directed against endothelial protein C receptors and scavenger receptor class B type 1 may induce endothelial cell activation.[112] The importance of the endothelium in facilitating leukocyte trafficking into the arterial wall, and how this might be targeted therapeutically, also remains to be determined.

Detection of smoldering arterial wall inflammation in LVV remains sub-optimal, especially in the face of normalized acute phase proteins. This highlights the urgent need for novel plasma and imaging biomarkers capable of sensitively and specifically identifying active disease, monitoring treatment-response, and distinguishing vascular and extravascular components of disease.[147, 241] Collaborative effort will facilitate collection of samples in sufficient numbers and diversity for application in novel technologies able to identify biomarkers and pathogenic pathways in complex autoimmune diseases. These include proteomic and metabolomic platforms, alongside genomic approaches such as single-cell and single-nucleus RNA-sequencing. While individual novel biomarkers may be unearthed, interest is focused upon the utility of clusters including metabolites.[242] A logistic regression model based on a group of eight cytokines has been reported to accurately distinguish active and inactive TAK,[243] while microRNA screening has revealed over-expression of pro-synthetic, and under-expression of contractile, microRNAs in TAB from patients with GCA.[244]

Recent developments in imaging technology, including the advent of total body PET, novel PET tracers, hybrid PET/MR scanners and high-resolution MRI, offer important opportunities for cardiovascular imaging. While ^{18}F-FDG-PET-CT has proved a sensitive and specific method for LVV diagnosis, its role in patient follow-up is less clear and recent studies have identified important caveats, suggesting additional PET tracers are required.[8, 245-247] Similar issues surround the interpretation of persistent MRI-detected arterial wall enhancement in LVV patients in apparent treatment-induced clinical remission.[188] A range of PET tracers is under investigation for their potential use in vascular inflammation imaging.[248] Much of this work is centred around atherosclerosis but may ultimately translate to vasculitis. Targets to explore in LVV include the TranSlocator PrOtein (TSPO) ligand[249, 250] and more recently, somatostatin receptor 2 using ^{68}Ga-DOTATATE and ^{18}F-FET-βAG-TOCA as part of an on-going PET/MR clinical study (NCT04071691).[251] The need to minimize radiation exposure, particularly for young patients remains paramount. New PET scanners limiting exposure times and increasing use of MRI are important steps in this direction.

An additional outstanding imaging challenge is the need to develop standardized and validated quantification techniques for non-invasive imaging,[245] such as those recently reported for MRI [252, 253] and ^{18}F-FDG-PET imaging.[246] Composite imaging scores suitable for use in patient monitoring and as defined end-points in clinical trials are urgently needed.

Multi-national studies will accelerate progress. Pooling of multi-centre imaging data has led to improved understanding of LVV phenotypic clusters,[254, 255] likely to lead to recognition of additional LVV subgroups.[150] Stratification, followed by prospective monitoring to investigate distinct patterns of risk and complications, will ultimately allow personalized treatment approaches. Moreover, homogeneity of subgroups is essential for future clinical trials.

Although the paucity of randomized, placebo-controlled clinical trials in LVV is well-recognized,[256] the landscape is changing (**Box 3**). Novel trial designs, such as that proposed for BIOVAS (Biologics in refractory vasculitis: A pragmatic, randomized, double-blind, placebo-controlled, modified-crossover trial of biologic therapy for refractory vasculitis) (https://fundingawards.nihr.ac.uk/award/17/83/01) may prove to be valuable. A significant additional hurdle in all these endeavours is the lack of widely accepted methods for grading disease activity, remission, and damage in LVV, a gap that the OMERACT group is trying to fill through the development of a core set of domains and outcome measures.[257]

Collaborative GWAS studies have yielded pathogenic insights and revealed potential therapeutic targets. Alongside identification of novel disease-susceptibility loci, prominent roles for NK cells, monocyte/macrophages, T cells and potentially B cells have been reported.[44, 49, 50, 258] In addition to reinforcing and extending identification of HLA risk factors and non-HLA susceptibility loci, a recent large multi-ancestral TAK GWAS identified additional candidate loci and devised a new genetic risk score.[49] Functional analyses of genetic variants identified are now required. Indeed, a TAK risk locus identified in *IL6* influences the monocyte anti-inflammatory gene *GPNMB* via chromatin looping and recruitment of an epigenetic repressive complex.[259]

Although significant challenges remain, progress is good, and prospects have never been better. Advances in the areas described will facilitate earlier diagnosis, better define disease remission, reduce morbidity and may allow development of GC-free therapeutic protocols and ultimately relapse-free treatment withdrawal for the majority of patients with LVV.

Table 1. LVV mimics

Infectious disease

- Bacterial infection
- Fungal infection
- HIV
- Q fever
- Syphilis
- Tuberculosis

Inflammatory disease

- Ankylosing spondylitis
- Atherosclerosis
- Behçet’s disease
- Clinically isolated aortitis
- Cogan's syndrome
- Cryoglobulinaemic vasculitis
- Granulomatosis with polyangiitis
- IgG4-related disease
- Polyarteritis nodosa
- Relapsing polychondritis
- Rheumatoid arthritis
- Sarcoidosis
- Systemic lupus erythematosus

Connective tissue disease

- Ehlers-Danlos syndrome
- Fibromuscular dysplasia
- Loeys-Dietz syndrome
- Marfan syndrome
- Neurofibromatosis
- Pseudoxanthoma elasticum

Congenital disease

- Aortic coarctation
- Mid-aortic syndrome

Neoplastic disease

- Erdheim-Chester disease
- Post-radiotherapy

• Immune checkpoint inhibitor therapy

HIV, human immunodeficiency virus

Table 2. Clinical features of GCA & TAK

Systemic symptoms	Symptoms of tissue/organ ischemia	Examination findings
• Anorexia • Arthralgia • Fatigue • Lethargy • Low grade fever • Myalgia • Sweats • Weight loss	• Abdominal pain† • Chest pain† • Cough* • Dyspnea† • Headache* • Jaw claudication* • Lightheadedness† • Limb claudication† • Neck pain* • Neurological deficit • Scalp tenderness* • Tongue claudication* • Vision disturbance*	• Aortic regurgitation† • Carotidynia† • Discrepancy between right and left arm BP • Hypertension† • Ophthalmic abnormalities* • Reduced or absent pulses† • Scalp tenderness* • Tender and/or thickened temporal arteries* • Vascular bruits

* More prevalent in GCA; † More prevalent in TAK [260]

BP, blood pressure

Table 3. Useful laboratory investigations for the diagnosis of LVV and exclusion of alternate diagnoses

Investigation	Rationale
	Recommended for all
FBC	'Reactive' FBC (*e.g.* thrombocytosis, normochromic normocytic anemia, leukocytosis) may reflect systemic inflammatory process
U&E	LVV rarely affects kidney function directly, but baseline results may help inform treatment
LFT	Non-specific abnormalities such as transaminitis or isolated raised alkaline phosphatase may be observed and may be misleading
Serum albumin	May be reduced secondary to systemic inflammatory process and can track recovery
CRP	Marker of inflammation, non-specific
ESR	Marker of inflammation, non-specific
	Additional tests, not recommended for all
ANCA	Useful to exclude small vessel vasculitis if part of differential
ANA	Non-specific, but useful to exclude alternate systemic inflammatory conditions if part of differential
RF / Anti-CCP	Useful to exclude RA if part of differential May detect cryoglobulinemia
Complement	May be elevated as part of inflammatory response; low C3 and/or C4 suggest alternative diagnoses (SLE, cryoglobulinemia, bacterial endocarditis)
Cryoglobulins	Useful to exclude cryoglobulinemia which may present with systemic features and may mimic large vessel inflammation
Serum immunoglobulins	Useful to exclude monoclonal gammopathy and IgG_4 related disease which may present with systemic symptoms and LV inflammation
Protein electrophoresis	Useful to exclude monoclonal gammopathy
Microbial investigations	If infection suspected clinically Hepatitis serology if PAN in differential diagnosis

FBC, full blood count; U&E, urea and electrolytes; LVV, large vessel vasculitis; LFT, liver function tests; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ANCA, anti-neutrophil cytoplasm antibodies; ANA, anti-nuclear antibodies; RF, rheumatoid factor; anti-CCP, anti-cyclic citrullinated peptide; RA, rheumatoid arthritis; PAN, polyarteritis nodosa

Table 4. Disease activity assessment tools

Tool	Study	GCA or TAK	Description	Validated in LVV
BVAS	Luqmani, 1994 [261]	Both	Designed to quantify disease activity for any vasculitis syndrome but only successfully validated in small vessel vasculitis and remains less applicable to LVV.	No
NIH criteria	Kerr, 1994 [262]	TAK	Combines clinical assessment, laboratory investigations and imaging; 74% correlation with PGA.[263]	No
DEI.Tak	Aydin, 2010 [263]	TAK	More detailed in certain aspects such as cardiovascular examination findings. Does not consider imaging or laboratory investigations and cannot easily distinguish active disease from established vascular complications.	Yes
ITAS and ITAS-A	Misra, 2013 [264]	TAK	Similar to DEI.Tak but with even greater weighting applied to cardiovascular involvement. ITAS-A also considers CRP & ESR. Validation in 177 patients showed good inter-rater reliability but correlation with PGA was limited.	Yes

GCA, giant cell arteritis; TAK, Takayasu's arteritis; LVV, large vessel vasculitis; BVAS, Birmingham Vasculitis Activity Score; NIH, National institutes for Health; DEI.Tak, Disease Extent index-Takayasu's arteritis; ITAS, Indian Takayasu Clinical Activity Score; ITAS-A, Indian Takayasu Clinical Activity Score-Activity; CV, cardiovascular; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PGA, physician global assessment.

Box 1. Mortality in GCA

A review of 17 studies – including 4,733 patients with a matched, general population control group – found an overall increase in mortality in GCA of ~20%.[56] Importantly, subgroup analysis demonstrated that this increase was confined to hospital in-patients, with no increase in the community setting. In line with this, a more recent UK-based community study of nearly 10,000 patients with GCA demonstrated an increased mortality in the first year following diagnosis, which was not sustained at five years.[265] A population-based study of >7,000 patients in Israel similarly observed increased rates of mortality within the first two years of diagnosis (that was not maintained at ten years follow up), and which was more pronounced in those presenting <70 years.[266] An Italian population-based study involving 281 patients with biopsy-proven GCA found reduced survival in those with large vessel involvement at diagnosis.[149] Similar results were observed in a US study of 204 patients with GCA, although survival was only reduced in those with aortic manifestations (as opposed to involvement of other large vessels only).[267]

Box 2. Advantages and disadvantages of different imaging modalities for LVV disease monitoring

Assessing response to treatment and monitoring vascular complications are important aspects of long-term disease management in LVV and can be achieved with a variety of non-invasive imaging techniques.[268] Interval ultrasound is rarely utilized for disease monitoring due to operator dependence and reliance on involvement of accessible vessels. MRI has the potential to be a useful tool, particularly as lack of radiation exposure permits interval scanning. Vessel wall-based metrics including mural thickness, increased mural signal and mural enhancement following administration of contrast may inform ongoing disease activity, though further study is required.[269] In a prospective study including 84 patients, correlation with clinical assessment of disease activity was less reliable with MR angiography than with PET, however, these modalities offered complementary information.[270] Vascular damage, including areas of previously identified stenosis or dilation, may be best monitored with MR angiography, with scoring systems now capable of quantifying vascular damage longitudinally.[252, 253] CTA may also be used for monitoring vascular damage but is less able to detect active disease once treatment has started.[271] CTA may be more useful when combined with PET, and although hybrid PET/CT is associated with more radiation exposure than CTA alone, this may be justified by the additional information gained. Grayson *et al* explored PET/CT as a disease monitoring tool in 56 patients with LVV and 59 comparators (a combination of healthy volunteers, disease 'mimics' and hyperlipidemic subjects) (**Figure 7**). They found a sensitivity of 85% and specificity of 83% for distinguishing active vasculitis from comparators.[127] PET/CT did, however, detect 'active' inflammation in 58% of patients who were in clinical-determined remission suggesting either an inability to distinguish active disease from vascular remodeling and atherosclerosis, or the presence of smoldering disease. This phenomenon has also been noted with other imaging modalities and remains a source of intense investigation. Such drawbacks mean that the role of PET/CT in disease monitoring remains far less established than for diagnosis. Hybrid PET/MR overcomes many of the problems associated with PET/CT and may provide a more detailed assessment of disease activity with reduced radiation exposure (~20% of PET/CT).[133, 134] PET/MR use is increasing in other cardiovascular disorders including coronary artery disease, cardiac sarcoidosis and cardiomyopathy.[272, 273] Data to support longitudinal PET/MR scanning over other imaging modalities are limited, but early results suggest feasibility and there is ongoing work on both sides of the Atlantic (**Figure 6**).[133, 274]

Box 3. Ongoing studies in GCA & TAK

GCA

Following demonstration of improved relapse-free survival in a phase 2 trial, an investigator sponsored phase 3 trial testing the efficacy of abatacept in GCA is in progress (NCT04474847).

As IL-1 is strongly expressed in GCA,[194, 275] and may have a significant role at multiple steps in the pathogenesis cascade, an investigator-sponsored phase 3 trial with anakinra (recombinant IL-1 receptor antagonist) is underway (NCT02902731).

IL-17 expression is increased in GCA and rapidly decreases with GC, indicating that IL-17 suppression by high dose GC may underline beneficial GC effects.[92] A phase 2 RCT blocking IL-17 with secukinumab is ongoing (NCT03765788).

IL-23, a heterodimer composed of p40 and p19 subunits, is a relevant cytokine in maintaining the Th17 differentiation pathway in GCA. The IL-23p19 subunit is expressed in excess over its partner IL12/23p40[276] and may have independent proinflammatory activities.[277] A phase 2 RCT neutralizing IL-23p19 with guselkumab is currently recruiting (NCT04633447).

IL-12/23p40 is expressed at low levels in GCA lesions.[276] Blocking IL-12p40 may reduce the activity of molecules related to Th1 and Th17 differentiation in GCA lesions.[276] Uncontrolled studies regarding the effect of ustekinumab, a monoclonal antibody against p40, have been inconclusive.[278, 279] Accordingly, a small, open label, investigator sponsored, phase 2 RCT trial is underway (NCT03711448).

In vitro data suggest a potential role for endothelin receptor antagonism as a means of inhibiting VSMC proliferation in LVV.[105] An open-label trial of bosentan in GCA has been proposed but is not yet recruiting (NCT03841734).

Phase 3 clinical trials of sirukumab and sarilumab (both of which target IL-6 activity) in patients with GCA were initiated but terminated early by the sponsor. Preliminary data with sirukumab showed positive trends.[280] An investigator-sponsored phase 3 trial comparing tocilizumab and MTX is ongoing (NCT03892785).

TAK

The efficacy of the JAK1 inhibitor, upadacitinib, is being evaluated in a phase 3, multicentre RCT in TAK (NCT04161898). An open-label randomised study comparing MTX with the JAK1/3 inhibitor, tofacitinib, in patients with mild/moderate TAK is also in progress (NCT04299971).

Following promising case series results, targeting the IL12/23p40 subunit with ustekinumab is to be evaluated in a phase 3 RCT (NCT04882072).

Lastly, a multicentre phase 2 RCT comparing tocilizumab with infliximab in patients with refractory or relapsing TAK is also planned and will hopefully provide much needed clarification regarding the efficacy of different biologic therapies in this patient group (NCT04564001).

Box 4. Patient perspective

Prior to diagnosis

By the evening of Christmas Eve 2018 I was very tired and feeling as if I had a virus. On Christmas day we walked along the beautiful promenade of the beach and I had to stop and rest at several benches on the way. In retrospect, I had pain in exactly the place where everyone who knows about it would say, ‘that person has temporal arteritis’.

I was unwell at home for a long time, eventually seeing my GP in February when the coughing, which had been keeping me awake at nights, showed no signs of abating and I still felt very unwell. The doctor prescribed a week of antibiotics. The symptoms lessened temporarily but a week later, they were worse. I had no energy and was not interested in food. I coughed and woke up spluttering more than once a night. I had nightly sweats; three nightdress nights were not unusual. My head was constantly ‘bunged up’. The GP prescribed nose spray with steroids in it. There was no noticeable change after using it. My hand was in the ‘temporal arteritis’ position very often. I then developed a rash all over my back and chest.

I was referred to the Bowel Clinic as my GP feared I had cancer. The Bowel Clinic suggested that, instead, I be referred to the General Medicine clinic. By this time, my family thought I was dying, and I could see in my GP’s eyes that he too was very concerned. In March, blood tests showed that I was anemic, and I was diagnosed with type 2 diabetes. I also had vision disturbances which the optician called visual migraines. By the time of the General Medicine appointment, I was aching all over with what the consultant said was polymyalgia rheumatica. She had to help me on to the couch and said that my spine revealed how much weight I had lost.

Following diagnosis

The specialist referred me for a PET scan, and I was diagnosed with large vessel vasculitis with thickening in the aorta. This meant nothing to me so I went home to Google. It was then that a colleague said to me, ‘My step-mother had that and almost lost her kidney and my friend was on chemo for another type of vasculitis.’ Suddenly I had a life-challenging disease. I read leaflets about vasculitis but, because it is rare, there was not one for large vessel vasculitis. I tried hard to get well, to be physically active and to eat well, but was exhausted most of the time. Showering and dressing sometimes was so tiring I went back to bed. I fell asleep often and had trouble getting up the stairs.

Starting treatment with steroids

For the polymyalgia rheumatica symptoms the steroids were a miracle cure. I was euphoric - out of pain in 2 hours after the first dose. After this, however, I felt out of control. My lips and fingers tingled, my body was ‘jangly’, and my mind became racy and out of focus. I spoke in an urgent way. I could not concentrate, could not organise myself. I was hungry, then very tired, and had to watch very bland, not challenging TV – nothing upsetting. Then the dip – 4 hours where I just did not care – about anything. EVERY SINGLE DAY. There were tears of course. The moon face, the ever-growing round stomach, the fatty lump on my arm and pouches of fat in odd places.

Reflections

Throughout the period of this illness, I saw a counsellor. I do not know how I would have managed without her. The counsellor helped me to face how hard it was to be ill, how much it changed me, how I struggled to work and how to plough on. I was able to talk about how out of control I felt, as if I was going mad. My 31-year-old daughter was also amazing in her support. She helped me to let go and accept that ALL I had to do was to focus on getting well, instead of thinking I was useless, incompetent and without a role in life.

I now feel strongly reassured by my rheumatologist, who supports me to remain calm about the continuing effects of taking steroids which, at this moment, I feel as if I might well be on for ever. Without this support I would be a very lost and bewildered 68-year-old, as I still cannot recognise this disease.

Figure 1. Disease classification and arterial involvement in LVV. Evidence from imaging studies and autopsy series has suggested significant overlap between C-GCA and LV-GCA such that many patients presenting with typical ‘temporal’ symptoms will have evidence of large vessel involvement if this is sought.[281] Although variation exists across the phenotypic spectrum of LVV, patterns of arterial involvement may help to distinguish LV-GCA and TAK. LV-GCA more commonly affects the axillary arteries, whereas TAK is more likely to affect the renal and mesenteric vessels.[281] Symmetrical involvement of arterial territories is usual with the possible exception of subclavian involvement in TAK (left subclavian more commonly implicated than the right).[282]

Figure 2. Global incidence of LVV. The regions studied include Alaska, USA (Mader 2009), Tennessee, USA (Smith 1983), Minnesota, USA (Salvarani 2004, Chandran 2015, Hall 1985) Ontario, Canada (Ing 2019), Argentina (Martinez 2016), Norway (Gran 1987, Brekke 2017, Gudbrandsson 2017), UK (Smeeth 2006, Watts 2009), Iceland (Tomasson 2019), Denmark (Boesen 1987, Dreyer 2011), Sweden (Mohammad 2015), Italy (Catanoso 2017), Slovenia (Pucelj 2019), Spain (Gonzalez-Gay 2007, Romero-Gómez 2015), Turkey (Saritas 2016), Israel (Friedman 1982, Bas-Landa 2007, Nesher 2016), Kuwait (el-Rasaid 1995), Australia (Dunstan 2014, Makin 2017), New Zealand (Abdul-Rahman 2011), Japan (Kobayashi 2003, Koide 1992), South Korea (Park 2017).

Figure 3. Proposed factors contributing to loss of immune privilege of large arteries and initiation of inflammation in LVV.

DC, dendritic cell; EC, endothelial cell; GCA, giant cell arteritis; LVV, large vessel vasculitis; MMP, matrix metalloproteinase; NOX2, NADPH oxidase 2; PD-1, programmed death-1; PD-L1, programmed death ligand-1; ROS, reactive oxygen species; TAK, Takayasu arteritis; T_{reg}, T regulatory cell.

Figure 4. Mediators of inflammation in LVV.

DC, dendritic cell; EC, endothelial cell; GM-CSF, granulocyte macrophage colony stimulating factor; ICAM-1, intercellular adhesion molecule 1; 1IFN-γ, interferon-gamma; IL-, interleukin; JAK, Janus kinase; MMP, matrix metalloproteinase; PDGF, platelet derived growth factor; PD-1, programmed death-1; PD-L1, programmed death ligand-1; ROS, reactive oxygen species; TLR, toll like receptor; TNF-α, tumour necrosis factor alpha; VCAM-1, vascular cell adhesion molecule 1; VSMC, vascular smooth muscle cell.

Figure 5. Approach to the investigation and diagnosis of LVV.

When considering the diagnostic approach to a patient with a primarily cranial presentation of LVV, clinicians should consider the pre-test probability of C-GCA, which will inform whether ultrasound or TAB is the most appropriate initial investigation (Mackie 2020). BP, blood pressure; C-GCA, cranial giant cell arteritis; CTA, computed tomography angiogram; LV-GCA, large vessel giant cell arteritis; LVV, large vessel vasculitis; MRA, magnetic resonance angiogram; TAB, temporal artery biopsy; PET, positron emission tomography; TAK, Takayasu's arteritis.

Figure 6. The utility of PET/MR in LVV. (A) Whole body MRA showing luminal subclavian abnormalities in a patient with TAK (arrows). (B) Fused coronal PET/MR image showing 18^{F}-FDG uptake involving subclavian arteries (arrows), aortic arch, and distal aorta (arrowheads) in a patient with LV-GCA. (C) Axial T1-vibe MR image with and without fused PET showing mural thickening (arrow) and 18^{F}-FDG uptake (arrowhead) within the thoracic aorta of a patient with LV-GCA.

Figure 7. Longitudinal follow-up imaging using 18^{F}-FDG PET. Images show a 68-year-old female patient with GCA at time of diagnosis (A) and at 6 (B) and 12 months (C) follow-up during treatment with tapered glucocorticoids and tocilizumab.

Figure 8. Flow diagram depicting the approach to management of LVV including novel therapeutic agents currently under investigation.

TAK, Takayasu arteritis; TNF, tumour necrosis factor; GCA, giant cell arteritis; MMF, mycophenolate mofetil; RCT, randomised controlled trial; GC, glucocorticoids.

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