

Monitoring and long-term management of giant cell arteritis and polymyalgia rheumatica

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Abstract | Giant cell arteritis (GCA) is the most common type of primary vasculitis in Western countries. Polymyalgia rheumatica (PMR) is the second most common inflammatory rheumatic disease of the elderly after rheumatoid arthritis. Glucocorticoids are the cornerstone of treatment for GCA and PMR, which are interrelated diseases. Glucocorticoids are effective, but adverse effects occur in a high proportion of patients. Careful use of glucocorticoids and the application of preventive strategies can minimize these adverse effects. Possible long-term complications of GCA include aneurysm and stenosis of vessels, even in patients with apparently clinically inactive disease; acute blindness is rare during glucocorticoid treatment. In PMR, whether subclinical chronic inflammation can lead to long-term damage is less clear. Management of both GCA and PMR is hampered by the lack of universally accepted definitions of remission and other disease states, such as low disease activity or vessel damage without active disease. In this Review, we outline current evidence on the monitoring and long-term management of patients with GCA and PMR, including the tapering of treatment.

Giant cell arteritis (GCA) is the most common type of primary vasculitis in Western countries^{1,2}. Polymyalgia rheumatica (PMR) is the second most common inflammatory rheumatic disease of the elderly after rheumatoid arthritis (RA)³. The two diseases are interrelated: 40–60% of patients with GCA have symptoms of PMR³, and histological features consistent with GCA have been found in 16–21% of temporal artery biopsy samples from patients with PMR³. Most of these patients with PMR, however, presented with additional features of GCA, whereas the prevalence of positive histology in unselected patients with PMR is unknown.

Both GCA and PMR are heterogeneous diseases. Although systemic manifestations (such as fever, malaise and weight loss) are common in both diseases, they are not present in all patients^{4–6}. Up to 1 in 5 patients with GCA with ocular involvement can present without systemic manifestations of the disease⁷.

GCA is the most common form of large-vessel vasculitis (LVV) and has a broad spectrum of disease manifestations, which are frequently overlapping. In the majority of cases, cranial and extracranial large arteries are involved to varying degrees, leading to different clinical phenotypes^{8,9}. Isolated cranial or extracranial GCA, which are at either end of this continuum, are relatively uncommon¹⁰. Predominant cranial GCA is characterized by headache, jaw claudication and visual manifestations

(representing the prototypical clinical picture of temporal arteritis). By contrast, predominant large-vessel GCA is characterized by more pronounced systemic manifestations, PMR, vascular bruits, limb claudication and imaging signs of inflammation in the aorta and its major branches¹⁰. In some of these patients, vascular stenoses or aneurysms in association with other GCA features are the presenting clinical manifestations^{9,11}. PMR is characterized by pain and stiffness in the shoulder and pelvic girdles, which can have an abrupt or a subtle onset³. Up to 20% of patients with PMR can present with a normal erythrocyte sedimentation rate (ESR)¹², although the presence of both normal ESR and C-reactive protein (CRP) levels is rare^{13–15}.

Glucocorticoids are the cornerstone of treatment for GCA and PMR. They are effective, but glucocorticoid-related adverse effects occur in up to 85% of patients with GCA and 65% of patients with PMR, respectively^{16–22}. The IL-6 receptor inhibitor tocilizumab has become available as a glucocorticoid-sparing strategy in patients with GCA^{23,24}, an approach that is also being evaluated for PMR^{25,26}. Management of both GCA and PMR is hampered by the lack of universally accepted definitions of remission and other disease states (such as low disease activity or vessel damage without active disease). Many questions about monitoring and long-term management are still unanswered (BOX 1).

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Key points

- Management of both giant cell arteritis (GCA) and polymyalgia rheumatica (PMR) is hampered by the lack of universally accepted definitions of remission and other disease states, such as low disease activity or vessel damage without active disease.
- Long-term management of GCA and PMR should be tailored to individual patient characteristics, including disease manifestations, as well as risk factors for treatment and disease-related complications.
- Imaging might help clinicians to monitor disease activity and damage; however, which imaging techniques to use and when to use them remains unclear.
- Although novel therapies such as anti-IL-6 agents help to reduce glucocorticoid exposure and achieve drug-free remission, questions remain about the best treatment regimens and biomarkers to monitor disease activity and predict flare after discontinuation of treatment.

In this Review, we outline current evidence on clinical and biochemical factors as well as imaging modalities for the monitoring and long-term management of patients with GCA and PMR, including the tapering of treatment and the handling of complications.

The natural history of GCA and PMR

GCA is a medical emergency because of the imminent risk of vascular complications such as blindness, stroke, limb ischaemia or aortic dissection or rupture. Vision loss has been reported to occur in 15–35% of patients with GCA; however, in the past few years, early recognition of the disease and immediate treatment with glucocorticoids seem to have reduced the incidence of GCA-related ischaemic complications^{27,28}. If vision loss in one eye has occurred, glucocorticoid therapy is nevertheless urgently required in order to prevent blindness in the second eye, which otherwise occurs in up to 50% of cases²⁹. Blindness in GCA is permanent and might be preceded by amaurosis fugax, diplopia, tongue pain or tongue necrosis and/or jaw claudication²⁹. The absence of these symptoms, however, does not preclude the occurrence of visual complications¹⁰. Patients with GCA who have a prominent inflammatory presentation — that is, those with high levels of CRP and ESR — seem to be at a lower risk of ischaemic complications^{4–6}. The development of aortic aneurysms is mostly a late complication occurring after several years of disease. Patients with GCA might develop aneurysms despite stable remission on or off treatment, indicating that mechanisms other than on-going vessel wall inflammation (such as disruption of the elastic lamina) might have a role^{30,31}.

PMR is characterized by an exaggerated systemic inflammatory response that is linked to soft-tissue inflammation in the neck, shoulder and pelvic girdle, as well as the spine³². Patients might also present with non-erosive arthritis in the shoulders and hips, and less commonly also at peripheral sites such as the knees and hands. Other peripheral manifestations include distal extremity swelling with remitting seronegative symmetrical synovitis with pitting oedema (RS3PE), tenosynovitis and/or carpal tunnel syndrome^{33,34}. Disease-related complications of PMR are less clear, unless patients develop clinically manifest GCA^{35,36}, which in turn might be associated with ischaemic and other complications. Whether PMR is self-limiting over time, or whether permanent remission can only be accomplished

by prolonged treatment with glucocorticoids with or without immunosuppressive agents, is a matter of on-going discussion.

Monitoring

Clinical monitoring

No widely accepted composite disease activity or disease state criteria exist for GCA and PMR, nor composite scores for the assessment of remission or relapse. In clinical studies, remission and relapse have mostly been defined by the authors of the respective trials as outlined in Supplementary Table 1. In GCA, the reappearance of fever, visual complaints, jaw or limb claudication, headache or PMR symptoms is usually considered consistent with relapse. In PMR, the reoccurrence of aching and stiffness in the pelvic and shoulder girdles are usually considered the cardinal features of a relapse. These symptoms should generally be accompanied by an increase in inflammatory markers to fulfil the definition of a relapse.

The Birmingham Vasculitis Activity Score (BVAS), developed for small vessel vasculitides, was prospectively assessed in a study of 136 patients with GCA³⁷. It does not capture principal manifestations of GCA such as tongue or jaw claudication, upper- or lower-extremity claudication and diplopia, and other items of the BVAS are not applicable to GCA, for instance, those regarding renal involvement³⁷. A modified version of the Vasculitis Damage Index, specifically adapted for LVV, has been proposed³⁸, but requires further validation. An on-going initiative of the Outcome Measures in Rheumatology (OMERACT) Vasculitis Working Group is to define the disease state and to select patient-reported outcome tools for LVV³⁹. A preliminary core set of outcomes for patients with LVV includes organ function, arterial function, biomarkers, fatigue, pain and death⁴⁰. A core data set to be collected from patients with GCA for clinical care and research purposes was published in 2019 (REF.⁴¹). This core set should improve consistency in the gathering of the data and serve as a guide to a standardized clinical evaluation, even in centres without extensive experience in GCA.

For PMR, a composite score called the PMR Activity Score (PMR-AS) has been proposed⁴². This score is based on the patient's pain assessment, physician's global assessment, morning stiffness, the ability of the patient to elevate the arms and CRP levels. A value of PMR-AS >17 identifies high disease activity, a value between 7 and 17 medium disease activity, a value between 1.5 and 7 low disease activity and a value <1.5 identifies remission⁴². Thresholds to define relapse have been proposed⁴³, but these measures are not widely used in clinical practice and trials. An OMERACT study group for PMR identified systemic inflammation (detected via laboratory markers), physical function, pain and stiffness as core outcomes that should be evaluated in all clinical trials and should be incorporated into a new score for assessing PMR disease activity⁴⁴.

Biomarkers

ESR and CRP are conventional laboratory markers for monitoring disease activity in GCA and PMR. In some trials, the recurrence of symptoms must be associated

Claudication

Cramping pain, elicited by repetitive activities (such as chewing or walking), owing to reduced blood flow.

Vascular bruits

An abnormal sound made on the auscultation of an artery, owing to a turbulent flow secondary to vascular stenosis.

Girdles

The parts of the appendicular skeleton that anchor the limbs to the axial skeleton, even though they are broadly defined as the shoulder and pelvis areas.

Amaurosis fugax

Transient visual loss (from the ancient Greek “ἀμαύρωσις”, meaning darkening, and the Latin “fugax”, meaning brief, fleeting).

Diplopia

The vision of two images of a single object (also called double vision).

Remitting seronegative symmetrical synovitis with pitting oedema (RS3PE). A clinical syndrome characterized by bilateral, diffuse swelling and inflammation of the hands and/or feet.

Box 1 | Unanswered questions in GCA and PMR and proposal for studies addressing these questions

- Should remission be defined clinically — including laboratory test results — or should imaging be part of the definition of remission?
 - Prospective study investigating the relevance of imaging compared to clinical findings for future outcomes such as relapses, disease-related and treatment-related damage, and quality of life.
- Is a treat-to-target strategy feasible and beneficial in giant cell arteritis (GCA) and polymyalgia rheumatica (PMR)?
 - Consensus project to define the treat-to-target concept in GCA and PMR.
 - Prospective study comparing treat-to-target versus conventional strategy with regard to outcomes.
- Which biomarkers should be used to assess disease activity when C-reactive protein and erythrocyte sedimentation rate are not reliable, for example, if IL-6 blocking agents are used?
 - Prospective study correlating alternative biomarkers such as osteopontin or calprotectin with clinical disease activity at different time points and at different disease activity states.
- Is a low-disease activity state acceptable in patients with GCA and PMR or should remission be achieved in all cases even if higher glucocorticoid doses are needed?
 - Prospective study comparing the effect of achieving remission versus low disease activity on outcomes such as future relapses, disease-related and treatment-related damage, and quality of life.
- Whether and how should imaging techniques be used in routine long-term follow-up to assess inflammation and vascular complications, such as aneurysm formation?
 - Long-term follow-up study of patients with GCA using a standardized treatment and imaging protocol in order to investigate the effect of imaging versus clinical assessment in regard to future relapses and detection and prediction of structural damage.
 - Prospective study comparing different imaging techniques and correlating them with clinical disease activity.
 - Prospective study comparing the outcome of treatment decisions based on clinical and imaging assessment versus clinical assessment alone.
- What are the clinical implications of persistent vascular abnormalities such as arterial wall thickening and tracer or contrast uptake detected with imaging techniques?
 - Prospective study investigating the relevance of subclinical imaging abnormalities for future outcomes such as relapses, disease-related and treatment related damage, and quality of life.

with an increment in inflammatory markers to be considered a relapse, whereas an isolated rise in acute-phase reactants is usually insufficient for defining a relapse (Supplementary Table 1). In our experience, patients often complain, during long-term follow-up, about the persistence of myalgia and fatigue despite normal ESR and CRP levels. In the clinic, assessing whether these symptoms are due to active inflammation or have other causes is often difficult. A relapse in the absence of raised CRP levels and ESR has been observed in 8 out of 39 relapse episodes (21%) in a cohort of 128 patients with GCA from The Vasculitis Clinical Research Consortium Longitudinal Study of GCA⁴⁵.

The assessment of possible relapse in the face of normal levels of acute phase reactants might be hampered in patients treated with anti-IL-6 receptor drugs, which can cause an apparent normalization of inflammatory markers even in the presence of active inflammation. In a sub-analysis of the GiACTA trial, almost all flares (92%) in tocilizumab-treated groups occurred with a normal level of CRP, whereas 34% of flares occurred with normal CRP levels in patients receiving prednisone alone⁴⁶. On the other hand, many patients receiving prednisone alone presented with elevated CRP levels without experiencing a clinical relapse.

In patients who have had PMR, an isolated increase in acute phase reactants without symptoms of PMR is usually insufficient to justify an increment of glucocorticoid dose, but persistently elevated CRP level raises suspicion of another underlying disease, such as GCA. In a prospective study of 94 patients with PMR⁴⁷, about 1 in 3 patients showed elevated levels of CRP in at

least one visit during the subsequent year of follow-up. Having a persistently increased CRP level was associated with an increased risk of developing clinical relapse or recurrence⁴⁷.

Collectively, ESR and CRP level have limited sensitivity and specificity in detecting a relapse in GCA and PMR. Because many clinical studies include an increment of inflammatory markers in the definition of relapse, assessing the performance of ESR and CRP for the detection of relapse is difficult when they are themselves part of the definition. This problem leads to circular reasoning (that is, testing a tool against a reference standard that includes the tool itself) and constrains interpretation of the disease state in those studies. An external standard, independent of acute phase reactants, should be used to better determine the role of ESR and CRP in evaluating disease activity. Plasma fibrinogen levels have been reported to correlate better with patient-reported outcomes than ESR and CRP in PMR, but the clinical utility of this parameter requires further evaluation⁴⁸.

Osteopontin, a glycoprotein with different functions in bone and immune homeostasis, has been tested as a possible biomarker in GCA⁴⁹. It is partially independent of the IL-6 axis and might therefore be applicable in patients receiving IL-6 blocking therapy. Although differences in osteopontin levels between treatment-naïve patients with active GCA and healthy control individuals were remarkable, the sensitivity of this parameter in detecting mild or moderate disease activity has not yet been tested. High baseline osteopontin levels have been associated with an increased risk of subsequent relapse⁴⁹.

Plasma calprotectin, also known as S100A8/A9, is another molecule that is regulated independently of IL-6 and might therefore be useful for monitoring GCA. Increased levels of calprotectin were detected in the adventitia and media of temporal arteries as well as in serum from patients with GCA⁵⁰, and mRNA expression of S100A8 (one of the two heterodimers of calprotectin, also denominated as calgranulin A or MRP8) was increased in temporal artery biopsy samples from patients with GCA with relapsing disease⁵¹. Monitoring studies investigating the change of calprotectin levels under therapy have been undertaken for patients with GCA receiving glucocorticoids (but not tocilizumab)⁵². In addition, in a cross-sectional study on 33 patients with RA treated with tocilizumab, levels of calprotectin were substantially lower in patients achieving remission than in those with active disease; on the contrary, ESR and CRP of these two groups were comparable⁵³. In 46 patients with GCA, those with active disease had higher levels of S100A8/A9 and S100A12 (the latter also known as calgranulin C) than patients with inactive disease⁵⁴. Limitations that might hinder the applicability of these measures in clinical practice include the fact that definitions of active and inactive disease were based on physician global assessment and the BVAS. In addition, the difference in biomarker levels between patients with active and those with inactive disease was small: 1,445.6 ng/ml versus 1095.7 ng/ml for S100A8/A9 and 163.2 ng/ml versus 116.6 ng/ml for S100A12, respectively⁵⁴.

Pentraxin 3 (PTX3) is a member of the pentraxins superfamily (the same family as CRP), a group of evolutionary conserved proteins involved in the innate immune response⁵⁵. Patients with recent optic nerve ischaemia due to GCA showed higher levels of serum PTX3 than patients with GCA without this manifestation⁵⁶. In patients with GCA receiving tocilizumab, PTX3 levels decreased during treatment⁵⁷. After 1 year, during clinical remission, patients with GCA had higher levels of serum PTX3 than healthy sex-matched and age-matched controls⁵⁷. This finding might suggest the persistence of on-going, subclinical vascular inflammation despite apparent clinical remission. On the contrary, in a group of 93 patients with PMR, PTX3 levels were comparable with those of healthy controls, both before and during treatment⁵⁸.

Other biological parameters that reveal dynamic change with therapy in GCA and PMR but have not been assessed for their practicability as disease activity or disease state measures include levels of neutrophils⁵⁹, CD8⁺ T lymphocytes^{60,61}, B cells⁶², regulatory T cells⁶³, T helper 1, T helper 17 and natural killer cells⁶⁴. An overview of the potential serological biomarkers for monitoring GCA and PMR is provided in TABLE 1.

Imaging

Imaging has an increasing role in the diagnosis of GCA⁶⁵ and PMR^{66,67}. Ultrasonography is a non-invasive and convenient technique that is increasingly used in the evaluation of patients with GCA and PMR. Other imaging modalities used to assess disease activity in GCA include sequential 18F-fluorodeoxyglucose

(FDG) PET with or without CT, contrast-enhanced CT or MRI. The role of advanced imaging for monitoring disease state and predicting disease outcomes is still uncertain. The typical appearance of chronic vasculitis during treatment with different imaging methods is provided in FIG. 1. An overview of the potential imaging biomarkers for monitoring GCA and PMR is provided in TABLE 1.

Ultrasonography in GCA. EULAR recommendations for the use of imaging in patients with LVV suggest that ultrasonography of the temporal artery (with or without the axillary arteries) should be the first imaging modality used in patients with suspected cranial GCA⁶⁵. The 'halo' sign, which is a homogenous, hypo-echoic wall thickening⁶⁸, is the pivotal ultrasonography sign in patients with GCA. However, it might be false-positive in ~5% of cases owing to examiner error or the presence of another disease such as lymphoma or severe arteriosclerosis^{69–71}. Although the halo sign at temporal arteries disappears in the majority of patients with GCA after 2–4 weeks⁶⁵, wall thickening of larger, extra-cranial vessels such as the axillary arteries might persist, at least for several months⁷². Chronic vasculitic changes seem to have a higher echogenicity than acute lesions, which might be because of the remodelling of the arterial wall⁷³. In one study, inflammatory wall thickening of the temporal and/or axillary artery was present in 19 out of 89 (21%) asymptomatic patients with GCA receiving glucocorticoid treatment⁷⁴. In another study of 42 patients with GCA⁷⁵, a reduction of vessel wall thickness following treatment was observed in 45% of patients at the level of the large arteries and in 85% of patients at the level of the temporal arteries. Patients with and those without a reduction of wall thickening differed neither in terms of relapses nor cumulative glucocorticoid dose at 1 year.

PET in GCA. Arterial FDG uptake usually decreases after glucocorticoid treatment is started^{76–78}; however, as many as 63–84% of scans show persistent uptake despite apparent clinical remission^{79–81}. A study of 37 patients with GCA and LVV undergoing repeated PET-CT suggested that patients without clinical improvement showed persistent abnormal vascular uptake, in contrast to those who experienced a clinical response, in whom FDG uptake decreased substantially⁸². Some PET studies indicate that patients with increased tracer accumulation in the large arteries are at an increased risk of a future clinical relapse⁷⁹, whereas persistent uptake in the aorta is a predictor of future aortic dilatation⁸³. Others have interpreted persistent FDG uptake as a sign of remodelling rather than persistent active inflammation. Although direct proof of this hypothesis is lacking, pathophysiological studies indicate that the acute inflammatory phase in GCA is followed by a phase of myointimal proliferation and growth of vascular microarchitecture that might lead to persistent wall thickening and on-going glucose consumption^{84–87}. This concept is supported by the histological evidence of persistent and/or chronic vasculitis, even in patients in apparent clinical remission. In a prospective study, 40 patients

Table 1 | Serological and imaging biomarkers for monitoring patients with giant cell arteritis and PMR

Biomarker	Pros	Cons
Serological biomarkers		
ESR ^{45–47,121}	Together with CRP, one of the most frequently used biomarkers for monitoring disease activity; widely available and inexpensive	Can be normal in >20% of patients with a relapse; influenced by many concomitant conditions (e.g. anaemia, age, infection, hypergammaglobulinaemia); false-negative results possible in patients treated with tocilizumab
CRP ^{45–47,121}	Together with ESR, one of the most commonly used biomarkers for monitoring disease activity; more specific than ESR; widely available	Can be normal in >20% of patients with a relapse; false-negative results in patients treated with tocilizumab; increased during infection
IL-6 ^{57,185–189}	Possible correlation with disease activity; in patients treated with tocilizumab, persistently high levels of IL-6 might predict future relapse	Strongly influenced by treatment with glucocorticoid and tocilizumab, as well as infections; low availability
Calprotectin ^{52,190}	More sensitive marker of inflammation than ESR and CRP; possible role for monitoring disease activity in patients treated with tocilizumab	Conflicting results about the effect of different treatments on calprotectin; limited availability for clinical use; limited experience and validation
PTX3 ^{56–58}	Possible relation with disease activity and recent optic nerve ischaemia	Similar levels in patients with PMR and healthy controls; limited availability
Osteopontin ⁴⁹	Possible correlation with disease activity; partially independent of the IL-6 axis	Limited availability
Imaging biomarkers		
US ^{72,74,75}	Enables evaluation of multiple arterial beds in single examination; no ionizing radiation; feasible and largely available	Unclear correlation between chronic signs of vasculitis and disease activity; examiner dependence
VHR-US ^{a191} or UHF-US ^b	Same as with standard US, plus the possibility of analysing intima, media and adventitia	Limited availability; unclear correlation between chronic signs of vasculitis and disease activity
CTA ⁹³	Short acquisition time; widely available	Persistence of wall thickening of unknown significance even in patients in remission; ionizing radiation and need for contrast medium
MRI or MRA ^{94–96}	Enables evaluation of vessel morphology (including aneurysm and stenosis); no ionizing radiation	Unclear correlation between persistent signs of vasculitis and disease activity; long acquisition time; generally only one vascular bed studied at a time; less readily available than US
FDG-PET-CT ^{76,81,91,114}	Possible correlation with disease activity; possible prediction of relapse after cessation of treatment and prediction of aortic dilatation; possibility of detecting other causes of inflammation (e.g. infection or cancer)	Significance of weak persistent vessel uptake despite absence of clinical activity is unclear; ionizing radiation; not universally available
FDG-PET-MRI ^{97,98}	Possible correlation with disease activity; possibility of studying vessel morphology (including aneurysm and stenosis) and detecting other causes of inflammation (e.g. infection or cancer)	Technical complexity of the acquisition and fusion protocols; very limited availability

CRP, C-reactive protein; CTA, computed tomography angiography; ESR, erythrocyte sedimentation rate; FDG-PET, 18F-fluorodeoxyglucose PET; MRA, magnetic resonance angiography; PMR, polymyalgia rheumatica; PTX3, pentraxin 3; US, ultrasonography; UHF-US, ultra-high-frequency ultrasonography; VHR-US, very-high-resolution ultrasonography. ^aPeak frequency of 55 MHz. ^bpeak frequency of 70 MHz.

with biopsy-proven GCA were randomly allocated to undergo a second biopsy at one of four time points, at 3, 6, 9 or 12 months⁸⁸. Overall, 24 out of 40 second biopsy samples (60%) revealed active arteritis, with 8 out of 18 (44%) showing active arteritis at 9 or 12 months. Medial fibrosis was present in 13 of the 40 specimens (33%) at baseline and in 24 of the 40 of second biopsy samples (60%). Other histological follow-up studies demonstrated that the footprint of GCA clearly persists in the temporal arteries^{87,89}, despite therapy: the density of inflammatory infiltrates and biomarkers of inflammation decrease, whereas biomarkers of vascular remodelling and fibrosis increase. Novel imaging modalities and specific tracers targeting the acute inflammatory response are warranted to disentangle the different phases of GCA. Preliminary evidence^{90,91} suggests that tocilizumab or methotrexate treatment might decrease vascular FDG uptake to a larger

extent than prednisone. In a cohort of 48 patients, 17% of patients receiving glucocorticoids showed no signs of vasculitis on follow-up PET-CT scans in comparison with 53% of patients receiving methotrexate or tocilizumab⁹².

CT in GCA. CT can reveal vessel wall thickening and contrast enhancement in patients with GCA⁷⁶. Of 35 patients with GCA treated with glucocorticoids undergoing baseline and follow-up CT scans (after a median of 13.5 months), 17 patients (48.5%) showed persistent arterial wall thickening on the second scan, mainly of the thoracic and abdominal aorta, despite clinical remission⁹³. Contrast enhancement was no longer present at follow-up in 15 of the 16 patients (93.75%) after 1 year of treatment. Whether further reduction of glucocorticoid dose or discontinuation of therapy would have resulted in reappearance of contrast enhancement is unclear.

MRI in GCA. MRI can depict vessel wall thickening and oedema, with contrast agent enhancement in the adventitia in patients with clinically active GCA. In a sub-analysis of a randomized trial of tocilizumab in patients with GCA, 9 patients receiving tocilizumab and 4 receiving placebo underwent baseline and follow-up MRI scans at 12 weeks and 52 weeks⁹⁴. All patients treated with tocilizumab were in clinical remission, but only 3 showed complete resolution of vascular abnormalities; 2 out of 4 patients receiving placebo were in clinical remission, and 1 of these 4 had complete resolution of imaging findings. Comparison studies^{95,96} suggest that FDG-PET might correlate better with disease activity than MRI, although the latter is more suitable for monitoring structural damage such as aneurysm and stenosis, as it provides morphological

rather than functional information. The strengths of these two techniques might be combined by the new hybrid PET-MRI machines^{97,98}, which are particularly appealing for the follow-up of patients with LVV, given the lower ionizing radiation exposure in comparison with PET-CT.

Ultrasonography in PMR. Typical ultrasonography findings in PMR are subdeltoid bursitis and biceps tenosynovitis, whereas trochanteric bursitis, glenohumeral and coxofemoral synovitis are less commonly detected⁹⁹. Although an early study suggested a corresponding decrease in clinical disease activity, laboratory markers and ultrasonography abnormalities during treatment¹⁰⁰, some lesions detected by ultrasonography, especially subdeltoid bursitis and biceps tenosynovitis, can persist, despite clinical remission^{66,101,102}. These findings might be related to degenerative disorders and their persistence does not necessarily imply a persistence of inflammation due to PMR. In one study, however, those patients who showed power Doppler signal in the articular and peri-articular shoulder structures at baseline had a higher frequency of relapse than those patients without evidence of power Doppler signal¹⁰¹.

PET in PMR. A study of 35 patients with PMR undergoing FDG-PET revealed a decrement in shoulder and hip uptake from baseline to 3 months after treatment, without further change at 6 months¹⁰³. In an open-label study of 20 glucocorticoid-naïve patients with PMR treated with tocilizumab²⁶, 18 also underwent serial PET-CT scans. FDG uptake decreased significantly at week 12 in all affected joint regions except for the shoulders and the interspinous cervical bursae¹⁰⁴, without correlation with clinical and biochemical parameters.

Other imaging techniques in PMR. Imaging techniques have been used in PMR mainly for diagnostic purposes and only rarely for monitoring purposes^{102,105}. A sub-analysis of ultrasonography and MRI changes, from the aforementioned study of tocilizumab in glucocorticoid-naïve patients with PMR²⁶, showed substantial improvement of all lesions, although none of the patients had complete resolution of all abnormalities at week 12 (REF. 66).

Long-term management

Predictors of disease course

Considerable variability exists in the disease course and response to therapy in patients with GCA. The presence of a strong inflammatory response at baseline — defined as the presence of at least three out of four items (fever, weight loss, high ESR and low haemoglobin level) — has been associated with protracted glucocorticoid therapy^{106,107}. Relapse rates are increased in patients who present at baseline with fever, marked inflammation on temporal artery biopsy samples and higher levels of inflammatory markers (ESR, CRP, serum amyloid A, haptoglobin and fibrinogen)^{108,109}. Starting treatment promptly at symptom onset is associated with a reduced risk of permanent vision loss, but is not associated with a lower (or higher) relapse rate¹⁰⁸.

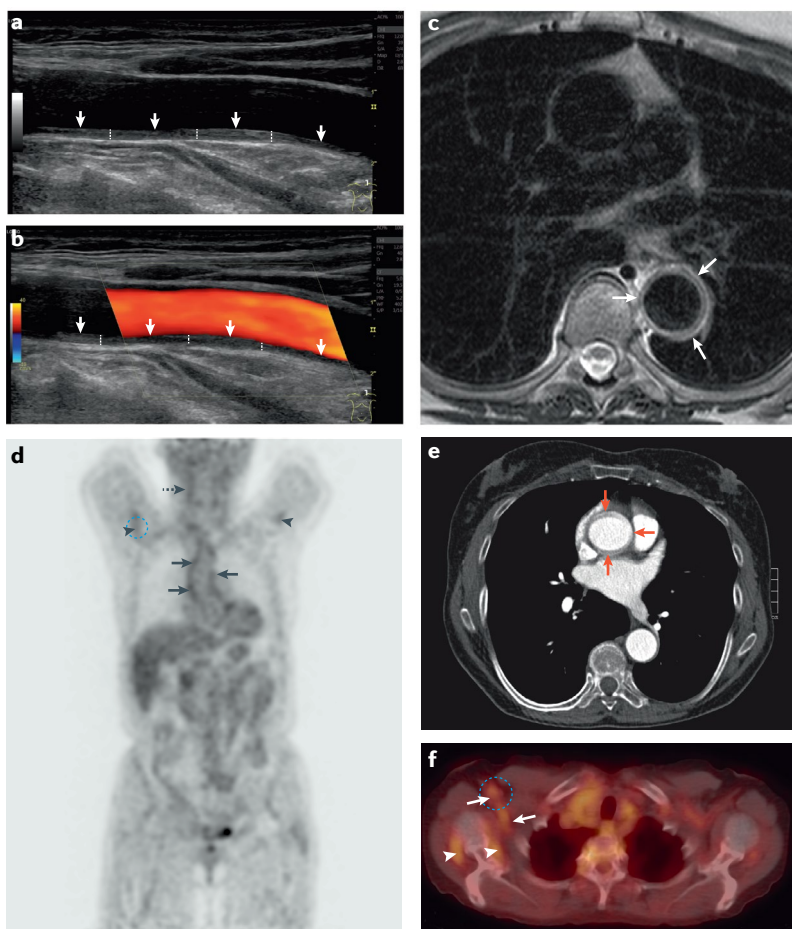


Fig. 1 | Imaging of chronic large-vessel vasculitis during glucocorticoid treatment. Different imaging techniques of the same patient, showing the appearance of chronic vasculitis during treatment. **a** | Ultrasonography, subclavian artery. The 'halo' sign (white arrows) with the typical homogenous and continuous wall thickening (white lines). The lamellar and hyperechoic pattern suggests chronic vasculitis. **b** | Same as panel **a**, with colour Doppler. **c** | MRI, axial view. Wall thickening and oedema of the descending aorta (white arrows). **d** | Fluorodeoxyglucose-PET, coronal reconstruction. Increased uptake of the ascending aorta (black arrows), the right carotid artery (dotted arrow) and of the axillary arteries (black arrowheads). **e** | Contrast-enhanced CT, axial view. Wall thickening of the ascending aorta (red arrows). **f** | Fluorodeoxyglucose-PET fused with CT, axial view (same scan as panel **d**). Increased uptake of the right axillary artery (white arrows). Capsular/peri-articular uptake of the right shoulder (white arrowheads), consistent with polymyalgia rheumatica. MRI images courtesy of M. Karner, Hospital of Brunico, Italy. PET images courtesy of M. Farsad, Hospital of Bolzano, Italy.

A sub-analysis of the GiACTA study¹¹⁰, which was a multivariate logistic regression analysis of pooled tocilizumab and placebo groups, indicated that a positive history of a CRP level >2.5 mg/dl was associated with an increased risk of treatment failure (defined as failure to achieve clinical remission by week 12 or occurrence of a flare between weeks 12 and 52). Female sex and a worse FACIT-Fatigue (a short self-reported questionnaire that measures the level of fatigue) score at baseline were also linked with an incomplete treatment response. The presence of LVV, determined either by CT angiography or PET-CT, has also been associated with an increased relapse rate¹¹¹.

In PMR, female sex, high levels of inflammatory markers, elevated platelet count and the presence of peripheral arthritis at the time of first presentation might be associated with an increased risk of relapse^{112,113}. Persistently elevated levels of CRP and IL-6 during follow-up have been associated with an increased risk of relapse and recurrence (that is, flare of PMR after discontinuation of glucocorticoid treatment)⁴⁷. Whether some of these patients had underlying GCA is unknown; however, imaging studies reported a high prevalence of underlying LVV in patients with PMR with recurrent flares^{114,115}. Surprisingly, patients with PMR who had subclinical LVV according to PET at baseline responded equally well to 15 mg daily prednisone and had a similar frequency of relapses to patients without vascular FDG uptake¹⁰³. Similarly, in a group of 66 patients with PMR undergoing serial clinical and ultrasonography assessment, remission and relapse were not associated with baseline articular findings on ultrasonography¹¹⁶. Routine vascular imaging of all PMR at baseline might therefore be less useful than in cases of recurrent flares or difficult-to-treat PMR, situations in which treatment decisions might be guided by the results of the imaging (FIG. 1).

Treatment with glucocorticoids

For both GCA and PMR, the current treatment approach consists of initial use of glucocorticoids, targeting the resolution of symptoms, followed by a gradual tapering of these agents^{112,117}. Current consensus is that as much glucocorticoid as necessary, but as little as possible, should be used¹¹⁸. In patients with GCA with visual manifestations, treatment with high-dose intravenous methylprednisolone (250–1,000 mg daily for 3 consecutive days) should be considered¹¹⁷. The 2018 update of the EULAR recommendations for the management of LVV suggest treating patients with GCA with an initial dose of prednisone 40–60 mg daily, to be tapered within 2–3 months to 15–20 mg daily, and, after 1 year, to ≤5 mg daily¹¹⁷. The same starting dose is suggested in the guidelines of the British Society for Rheumatology (BSR) on the diagnosis and treatment of GCA, whereas the tapering schedule is slightly different: after initial remission induction, prednisone is tapered by 10 mg every 2 weeks until 20 mg, then by 2.5 mg every 2–4 weeks until 10 mg, and then by 1 mg every 1–2 months, provided that remission is maintained¹⁰⁷.

High-quality evidence concerning the most effective tapering schedule in patients with GCA is lacking.

The two placebo arms of the GiACTA trial compared a 26-week versus a 52-week prednisone tapering schedule²³. After 52 weeks, 7 (14%) patients in the group in which tapering was rapid achieved sustained remission versus 9 (18%) patients in the group in which tapering was slower. Thirty-four (68%) patients in the first group experienced relapse versus 25 (49%) in the second group⁴⁶. These data suggest that slower tapering is associated with fewer cases of relapse. In current clinical practice it is unusual for patients with GCA to be treated for ≤6 months because of the frequency of disease relapse after this period of time; standard treatment regimens are for >1 year. The tapering strategy should be individualized on the basis of the risk of relapse and the risk of glucocorticoid-related adverse effects, choosing the minimal effective dose that maintains remission with an acceptable burden of adverse effects. Notably, management strategies are rapidly evolving with the introduction of anti-IL-6 therapies.

According to one small randomized study, induction therapy with intravenous methylprednisolone pulse therapy (15 mg/kg body weight for 3 days) in patients without eye symptoms reduced the relapse rate and cumulative glucocorticoid dose (if pulses are not counted), and led to a higher number of patients in remission while receiving ≤5 mg prednisone per day at weeks 36–78 (REF: ¹¹⁹). In another study, no difference was observed concerning discontinuation of glucocorticoids or cumulative glucocorticoid dose at 12 months between groups receiving a single pulse of 240 mg methylprednisolone and those who did not¹²⁰. Owing to the controversial data and the fact that the positive trial had some methodological limitations, such as small sample size and a relapse definition that was fulfilled by increment of acute phase reactants alone, EULAR recommendations preclude the use of intravenous pulse glucocorticoid therapy in patients with uncomplicated GCA for the purpose of reducing relapses or cumulative glucocorticoid dose¹¹⁷.

In PMR, the starting prednisone dose should be 12.5–25 mg daily, to be tapered to a dose of 10 mg daily within 4–8 weeks and, thereafter, the daily dose should be decreased by 1.0–1.25 mg daily every 4 weeks¹¹². However, only ~50% of patients might have a complete resolution of symptoms after 4 weeks of treatment¹²¹. In selected patients, intramuscular methylprednisolone (initial dose: 120 mg every 3 weeks) might be used as an alternative to oral glucocorticoids¹¹². One randomized controlled trial (RCT) demonstrated that intramuscular methylprednisolone led to a lower cumulative glucocorticoid dose and lower weight gain at week 96 than oral glucocorticoids, whereas the clinical efficacy of both strategies was comparable¹²².

Adjunctive therapies

The 2018 update of the EULAR recommendations for the management of LVV and the guidelines of the BSR suggest starting tocilizumab in patients with GCA with refractory or relapsing disease or as initial therapy in patients at risk of glucocorticoid-related adverse events, such as those with diabetes, osteoporosis or a high-risk cardiovascular profile^{107,117}. Tocilizumab should be given

concomitantly with glucocorticoids, as data are insufficient to support tocilizumab monotherapy as the initial treatment. The recommendation for the use of tocilizumab in GCA is mainly based on the results of the GiACTA trial, in which patients receiving tocilizumab had a higher rate of glucocorticoid-free remission at 1 year than patients treated with glucocorticoids only²³. In this study, flare was defined as the recurrence of signs or symptoms of GCA and an increase in ESR ≥ 30 mm/h, attributable to GCA, in association with the need for increasing prednisone dose. Remission was defined as the absence of flare and a CRP level < 1 mg/dl. Both ESR and CRP levels were blinded to the investigators in this trial. Sustained remission was defined as remission from week 12 through to week 52 without the need to increase the glucocorticoid dose of the pre-specified tapering schedule (Supplementary Table 1). After 1 year, 56% of the patients treated with tocilizumab weekly and 53% of those treated with tocilizumab every other week were in sustained remission, in comparison with 14% of those receiving placebo plus the 26-week prednisone tapering regimen and 18% of those receiving placebo plus the 52-week prednisone tapering regimen²³. Evidence regarding the minimal dose of glucocorticoids needed in patients treated with tocilizumab is unclear. Tapering of glucocorticoids should be individualized, taking into account that ESR and CRP are often not reliable indicators of disease activity in patients receiving tocilizumab. The results of the trial suggest that glucocorticoids can be withdrawn as early as after 6 months. However, given the lack of data on the long-term effect of tocilizumab on vascular damage and other complications, this short schedule might be appropriate only in patients with severe adverse effects from glucocorticoids.

Several studies (albeit with lower quality than the GiACTA trial) have suggested that methotrexate might have a modest effect in reducing the number of relapses in patients with GCA when used in combination with glucocorticoids¹⁰⁶. A meta-analysis pooling the individual data of the three methotrexate trials in GCA reported that patients in the methotrexate group had a modest reduction of the risk of a first and second relapse up to 48 weeks, increased rates of glucocorticoid-free remission and reduced cumulative glucocorticoid doses¹²³. According to the EULAR and BSR recommendations, methotrexate might be an alternative to tocilizumab for glucocorticoid sparing in GCA^{107,117}.

The 2015 American College of Rheumatology/EULAR recommendations for the management of PMR¹¹² suggest the use of methotrexate for patients at high risk of relapse, prolonged treatment and glucocorticoid-related adverse events, as well as in those patients with a refractory course of the disease. This recommendation was based on the results of four RCTs¹²⁴. One of these RCTs studied 62 patients with PMR and showed a higher rate of glucocorticoid discontinuation after 76 weeks in the glucocorticoids plus methotrexate group than in the glucocorticoid plus placebo group¹²⁵. The 6-year follow-up of this study, however, revealed a similar incidence of glucocorticoid-related adverse events in both groups, in spite of a lower cumulative glucocorticoid dose in patients who received

methotrexate¹²⁶. The other three trials yielded conflicting results, with an absent or unclear benefit of methotrexate. However, these studies have substantial methodological limitations¹²⁴.

The role of anti-IL-6 treatment for PMR has been evaluated in several small, open-label studies with a duration of 24 to 52 weeks^{25,26,127–129}. In aggregate, these studies with a total of 53 patients suggest that anti-IL-6 therapy might be associated with lower glucocorticoid doses and lower rates of relapse than glucocorticoids alone, although symptom relief seemed to occur sooner in glucocorticoid-treated patients. Three of these studies assessed tocilizumab monotherapy^{26,128,129}. In one of the studies¹²⁹, 9 out of 13 (69%) patients achieved remission with tocilizumab monotherapy at 1 year. In the other studies, concomitant glucocorticoid therapy seemed to be necessary to achieve complete remission^{26,128}. An RCT comparing sarilumab plus glucocorticoid (tapered over 14 weeks) with placebo plus glucocorticoid (tapered over 52 weeks) (NCT03600818) is ongoing¹³⁰.

Tapering treatments and managing relapses

In the 2018 update of the EULAR recommendations for the management of LVV the goal of a prednisone dose ≤ 5 mg daily after 1 year of treatment in patients receiving glucocorticoid monotherapy is suggested, whereas in the BSR guidelines discontinuation of glucocorticoids after 12–18 months is targeted^{107,117}. The tapering of glucocorticoids can be much faster (down to zero within 26 weeks according to the GiACTA study²³) in patients receiving tocilizumab. In patients receiving glucocorticoid monotherapy, it usually takes even longer than 1 year to achieve a low daily glucocorticoid dose for a sustained period. A study from a German database showed that patients with GCA were receiving ≤ 5 mg daily prednisone 18–24 months after diagnosis and, after 3 years, they were still taking a daily prednisone dose between 4–5 mg (REF.¹³¹).

In a population-based inception cohort from the Rochester Epidemiology Project¹³², patients diagnosed with GCA between 1950 and 1979 received a lower cumulative glucocorticoid dose and had a higher probability of discontinuing glucocorticoids than those diagnosed in the 1980–2009 period. The authors suggest that this trend towards higher glucocorticoid doses in modern times might be related to a greater awareness of GCA and its complications or to the extensive use of imaging, which might have disclosed subclinical LVV in a considerable proportion of patients¹³².

Relapses are frequent during tapering and after cessation of treatment for GCA. Up to half of patients with GCA treated with glucocorticoids alone have at least one relapse¹³³. During the first year of the GiACTA trial, 36 out of 149 (24%) patients receiving glucocorticoids plus tocilizumab had a flare, in comparison with 59 out of 101 (58%) receiving glucocorticoids plus placebo⁴⁶. The majority of flares occurred while patients were taking a prednisone dosage ≤ 10 mg daily in both groups. However, 25% of flares in those receiving glucocorticoids plus tocilizumab, and 22% of flares in those receiving glucocorticoids plus placebo, occurred while patients were taking > 10 mg prednisone daily. After 1 year,

117 out of 149 patients who initially received tocilizumab were in clinical remission (79%), and 51 of these patients (44%) maintained clinical remission over the following 2 years. Among these 51 patients in clinical remission, 33 (65%) were no longer receiving tocilizumab or glucocorticoids. In comparison, among the 67 patients receiving glucocorticoids plus placebo who were in remission at week 52, a total of 38 (57%) were still in remission 2 years later. 17 of these 38 patients (45%) were in treatment-free remission²⁴.

Similar results were reported from the phase II study on tocilizumab¹³⁴, in which 17 of the 20 patients

who received tocilizumab and were in treatment-free remission after 1 year were followed up. Eight out of 17 patients (47%) had disease relapse after a mean of 6.3 months (range 2–14), the majority during the first 5 months after tocilizumab withdrawal¹³⁵. Despite the evidence regarding the higher percentage of remission in patients with GCA treated with tocilizumab, uncertainty remains about which patients are more likely to benefit from tocilizumab, for how long tocilizumab should be continued and whether it is also effective in preventing vascular structural damage (for example, aneurysm). Considering the lower overall glucocorticoid exposure and the high remission rates in the GIACATA trial, the question arises whether anti IL-6 therapy with or without glucocorticoids should be used in every patient with GCA. Cost-effectiveness studies along with long-term safety data from real-world practice are needed before a clear recommendation can be made on this issue.

In PMR, the estimated relapse rate is about 31.5 per 100 person-years, and is higher in the first months of the disease¹³⁶. A population-based study from Olmsted County of 359 patients with PMR reported that the median time to reach a daily prednisone dose <5 mg, for at least 6 months, was 1.44 years (95% CI 1.36–1.62)¹³⁶. The median time to achieve permanent withdrawal of glucocorticoids was 5.95 years (95% CI 3.37–8.88). A review on the tapering and discontinuation of treatments in PMR found substantial heterogeneity in the published literature, owing to different study design, patient selection and tapering schedule¹³⁷. Overall, about half of the patients could discontinue glucocorticoids after 2 years of treatment, with wide variation among studies (ranging from 24% to 96%)¹³⁷. About 1 in 5 patients needed glucocorticoid therapy for >4 years¹³⁷. In the Olmsted County study, only 58% of patients could discontinue glucocorticoid therapy after 10 years¹³⁶. Recurrence of the disease, defined as the reappearance of symptoms and laboratory abnormalities after the cessation of therapy, occurred in 10–30% of patients¹³⁷. Other reasons why tapering of glucocorticoids might be challenging in GCA and PMR are the worsening of non-inflammatory conditions such as shoulder or hip osteoarthritis as well as adrenal insufficiency. One study reported adrenal insufficiency in 15% of patients with PMR or GCA after glucocorticoid treatment for >5 months, and recovery of adrenal function only occurred in some patients after discontinuation of glucocorticoids¹³⁸.

In both GCA and PMR, the treatment of relapse is usually managed by increasing the glucocorticoid daily dose to the last effective dose^{107,112,117} or by increasing the glucocorticoid dose by 5–10 mg, especially when patients are taking low-dose glucocorticoids (for example, prednisone <5 mg daily) at the time of the relapse. In the case of a major relapse of GCA — defined by EULAR as recurrence of active disease plus clinical features of ischaemia or evidence of active aortic inflammation with progressive aortic damage, and by BSR as relapse associated with ischaemic manifestations — glucocorticoids should be increased to the initial dose (40–60 mg prednisone daily)^{107,117}. A selection of common clinical scenarios, and their management, in the long-term follow-up of patients with GCA and PMR, is provided in FIG. 2.

GCA and/or PMR

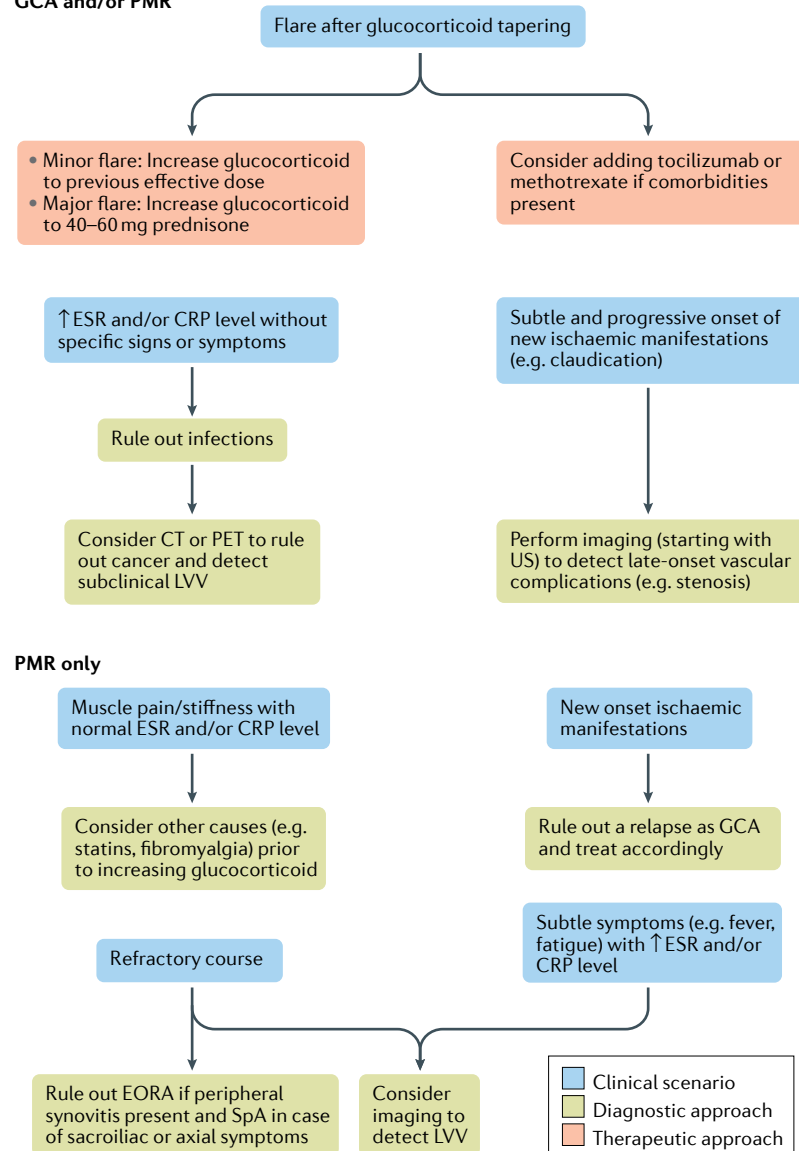


Fig. 2 | Common clinical scenarios, and their management, in the long-term follow-up of patients with GCA and PMR. The upper part of the flow chart is applicable to patients with giant cell arteritis (GCA) and/or polymyalgia rheumatica (PMR); the lower part refers specifically to patients with PMR only. A major flare is defined as recurrence of active disease plus clinical features of ischaemia or evidence of active aortic inflammation with progressive aortic damage. A minor flare is defined as recurrence of active disease, not fulfilling the criteria for a major relapse¹¹⁷. CRP, C-reactive protein; EORA, elderly-onset rheumatoid arthritis; ESR, erythrocyte sedimentation rate; GC, glucocorticoid; LVV, large-vessel vasculitis; SpA, spondyloarthritis; US, ultrasonography.

Is a treat-to-target approach possible?

A treat-to-target approach is based on pursuing a pre-determined treatment outcome. This approach is predicated on the ability to monitor disease state regularly and adjust therapies with the aim of achieving specified results, such as remission or low-disease activity. Although specific guidelines on treat-to-target in GCA and PMR have not been developed, factors that might guide treatment decisions include clinical symptoms, serological markers and imaging results (while recognizing that clinical remission is not necessarily concordant with remission on imaging)¹³⁹. Current guidelines do not include the concept of a remission–induction phase followed by a remission–maintenance phase as in other vasculitides. Moreover, whether remission should be obtained ‘at any cost’ or if low disease activity might be an acceptable target, especially in patients with substantial treatment-related adverse effects, is an open question.

Disease and treatment complications

Long-term complications of GCA include arterial dilatations and aneurysms. Evaluation of vascular disease in GCA is challenging because the disease itself and the consequences of prolonged glucocorticoid therapy, as well as age and comorbidities such as atherosclerosis, can cause vascular damage. Numerically, more patients with GCA experience complications from glucocorticoid treatment than from the disease itself⁶⁸.

A retrospective study from England, which analysed data from patients with GCA and PMR registered in family practices¹⁴⁰, documented a substantial increase in the risk of infections, even in patients taking 5 mg prednisone per day, a glucocorticoid dose that is considered to have an acceptable safety profile¹⁴¹. In this record-linkage study, however, no effort was made to adjust the results for confounding by indication. This approach is necessary because glucocorticoid doses are linked to clinical activity, and increased disease activity is associated with an increased risk of infections in several rheumatic diseases^{142–147}.

A USA claims-based analysis of 2,497 patients¹⁹ with GCA showed an overall adverse event rate of 0.43 events per patient-year; cataract and osteoporosis were the most frequent adverse events. Increased glucocorticoid exposure was associated with bone-related adverse events, cataract, glaucoma, pneumonia and diabetes mellitus¹⁹.

Early studies reported a high incidence of glucocorticoid-related adverse events in PMR, with up to 65% of patients experiencing at least one glucocorticoid-related adverse event²¹. A meta-analysis reported the following adverse event rates per 100 patient-years in patients with PMR: 14 gastrointestinal; 12 cardiovascular; 12 endocrine or metabolic; and 11 infectious adverse events¹⁸. Three of the four studies evaluated in this meta-analysis, however, were published >20 years ago. Prevention strategies for glucocorticoid-related adverse events (such as prescription of proton pump inhibitors in patients concomitantly using NSAIDs and screening and treatment of cardiovascular risk factors or osteoporosis)^{141,148} were less developed at that time. A 2018

systematic review of the incidence of new-onset diabetes mellitus in patients with GCA and PMR (with a weighted mean age of 74.1 years) identified a cumulative incidence of 13% (95% CI 9–17%) and 6% (95% CI 3–9%), respectively, an incidence higher than expected at that age group¹⁴⁹.

In contrast to the aforementioned reports, a population-based study from Olmsted County did not find, except for cataracts, a higher incidence of glucocorticoid-related adverse events in patients with PMR in comparison with a randomly selected cohort of patients, with similar age and sex distribution, without PMR¹³⁶. The explanation for the difference between this and previous studies is not yet clear; careful management of low-dose glucocorticoids with regular screening for and prevention of glucocorticoid-related adverse effects might have led to an overall acceptable safety profile of glucocorticoids, even in the long term. A compilation of glucocorticoid complications occurring with long-term use, and possible strategies for prevention, screening and management is provided in TABLE 2. The Glucocorticoid Toxicity Index might assist clinicians assessing the risk–benefit of long-term glucocorticoid treatment¹⁵⁰.

Patients with GCA are at a higher risk than the general population of developing aneurysms, especially of the thoracic aorta, and aortic dissection^{151–154}. However, a wide range of prevalence of thoracic aortic aneurysms is reported in the literature, with estimates of 2–18% of patients with GCA^{155,156}. This variety in the prevalence might be attributable to differences in study design, aneurysm definition and ascertainment (imaging versus surgical procedures), as well as to the different populations studied. In a prospective follow-up study from Spain, for example, focal (saccular or fusiform aneurysm) or diffuse aortic dilatations (≥ 4 cm in the thoracic and ≥ 3 cm in the abdominal aorta) were observed in 22.5% of patients after a median follow-up of 5.4 years and in 33.3% of patients after 8.7 years^{30,31}. In Sweden, the overall incidence of thoracic aortic aneurysm, dissection and rupture has been estimated at 0.16 per 1,000 person-years in men, and 0.09 per 1,000 person-years in women¹⁵⁷. Overall, the estimated incidence of thoracic aortic aneurysms in GCA is 1–10 per 1,000 person-years¹⁵⁶. On average, about 7 patients with GCA would need to be screened to detect 1 case of dilatation or aneurysm of the thoracic aorta¹⁵⁶.

The development and progression of aneurysms seem to be associated with traditional atherosclerotic risk factors^{155,158,159} and inflammation as assessed by imaging^{160,161}. In fact, the presence of FDG uptake detected by PET–CT has been associated with subsequent aortic dilatation¹⁶⁰. In a retrospective study of 549 patients with GCA, the presence of cranial signs of GCA was inversely associated with the development of aortic dilatation¹⁶¹. This finding further supports the notion of several overlapping clinical patterns in GCA with different disease trajectories^{9,10}. Histological studies suggest that a disarray of elastic fibres is the most prominent finding in GCA-related aortic aneurysms, whereas active inflammation is inconsistently found^{30,162}. Histological evidence of active aortitis, however, seems to be closely associated with aortic dissection or rupture¹⁶³. The

Table 2 | Glucocorticoid complications and strategies for prevention, screening and treatment

Complication	Prevention	Screening	Treatment
Osteoporosis	Anti-resorptive therapy and vitamin D; physical activity; smoking cessation; dietary interventions	BMI; serum levels of PTH, 25-OH-vitamin D; albumin and serum calcium levels; DXA scan	Anti-resorptive or anabolic therapy and vitamin D with or without calcium supplements ^a
Hyperglycaemia	Physical activity; dietary interventions	BMI; serum levels of glucose and HbA _{1c}	Add a glucocorticoid-sparing agent to decrease glucocorticoid daily dose; glucose-lowering drug
Hypertension	Physical activity; dietary intervention; smoking cessation	BMI; blood pressure measuring ^b	Anti-hypertensive medication; add a steroid-sparing agent to decrease glucocorticoid daily dose
Dyslipidaemia	Physical activity; dietary intervention; smoking cessation	Serum levels of total cholesterol, HDL-C, LDL-C and triglycerides	Lipid-lowering drug ^c
Weight gain	Physical activity; dietary intervention	BMI	Add a steroid-sparing agent to decrease glucocorticoid daily dose; consider treatment with intramuscular methylprednisolone in patients with PMR (which may lead to lower weight gain than oral glucocorticoid treatment)
Infection	Vaccination; smoking cessation	Mantoux test or IGRA ^d ; serology for hepatitis ^d	Prophylaxis for tuberculosis and infective hepatitis ^e ; withdrawal of DMARDs in the case of severe infection; possible reduction of glucocorticoid dose according to the underlying infection

DXA, dual X-ray absorptiometry; HbA_{1c}, haemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; IGRA, interferon- γ release assays; LDL-C, low-density lipoprotein cholesterol; PMR, polymyalgia rheumatica; PTH, parathyroid hormone. ^aAccording to local guidelines. ^bConsider home blood pressure monitoring according to patient's profile and local guidelines. ^cSpecial considerations may be applied to patients receiving tocilizumab for its possible effect of increasing lipid levels. ^dThese tests should be considered especially in patients receiving high-dose glucocorticoid and/or other DMARDs, either synthetic or biologic, owing to their significant immunosuppressive effect.

recommendations of the French Study Group for LVV suggest screening for vascular complications with CT or MRI at diagnosis and thereafter every 2–5 years¹⁶⁴. This recommendation is mainly based on consensus, as evidence on this issue is limited. Whether patients with PMR and subclinical vasculitis might eventually develop aneurysms is not clear. Among a cohort of 350 patients with PMR, 50 developed thoracic aortic aneurysm or dilatation, despite presenting with similar cardiovascular risk factors to those without this complication¹⁶⁵.

An increased risk of myocardial infarction, cerebrovascular accident and peripheral vascular disease has been reported in patients with GCA^{166,167}, possibly related to an increased burden of vascular disease and comorbidities already present before the diagnosis of GCA¹⁶⁸. Although retrospective data suggest that anti-platelet or anti-coagulant agents might decrease the risk of ischaemic events in patients with GCA^{169,170}, the addition of these agents to glucocorticoids at the time of diagnosis has not been demonstrated to reduce GCA-related complications. Consequently, the 2018 update of the EULAR recommendations and the BSR guidelines suggest the use of anti-platelet or anti-coagulant drugs, only if indicated by the general cardiovascular profile of the individual patient, but not to treat GCA itself^{107,117}.

In PMR, data on the risk of coronary artery¹⁷¹ and peripheral vascular¹⁷² disease seem to be controversial: although some studies reported an increased risk in patients with PMR, others found the risk to be

comparable with that of the general population^{173,174}. Patients with PMR should therefore receive cardiovascular management on the basis of their individual risk profile.

Overall survival of patients with GCA and PMR seems to be comparable with that of the general population^{155,175–178}. By contrast, patients with GCA with vascular complications such as aneurysms or dissection have a much higher mortality than patients with GCA who do not have these complications^{31,154}.

Conclusions

New onset GCA is a medical emergency that warrants immediate treatment with glucocorticoids, given the possible devastating complications such as blindness, stroke or aneurysm and dissection. In the long term, management of GCA and PMR should be adapted on the basis of individual patients' characteristics, including risk factors for treatment-related and disease-related complications, considering that, numerically, more patients will experience a complication due to glucocorticoids than the diseases themselves. The long-term management of patients with GCA and PMR should be based on a combined evaluation of the clinical presentation, patient's complaints and serological and imaging biomarkers and should include regular screening and prevention of glucocorticoid-related adverse events. Important to the research agenda for clinical management and trials in GCA is the development of scores and definitions for disease states.

Imaging might help clinicians to monitor disease states and damage; however, questions remain about when and which imaging technique to use. Imaging can be helpful when a clinical relapse is suspected and when inflammatory markers are persistently activated. It can also be useful for monitoring vascular damage. A pragmatic approach might be to perform an imaging examination, starting with ultrasonography and followed by MRI or PET-CT, in all patients with GCA at baseline and thereafter, every 2 to 3 years, to detect vascular complications. Such an approach, however, is not evidence-based and, in patients with multiple traditional cardiovascular risk factors, screening for aneurysms might be needed more frequently. In patients with PMR, advanced imaging such as PET-CT can be considered in the case of a refractory disease course and when clinical or serological hints of persistent inflammation are present, to detect a possible LVV.

Tocilizumab is now approved for GCA and helps to reduce glucocorticoid exposure and achieve drug-free remission. Questions remain as to whether it should be started at baseline in all or selected patients, for example, in those at a high risk of glucocorticoid-related adverse

events, or whether it should be added only in patients with refractory disease or when glucocorticoid-related adverse events occur. Furthermore, the duration of tocilizumab therapy is not established; after cessation of tocilizumab treatment only ~50% of patients remain in remission and, unfortunately, we still do not have good biomarkers for predicting which patients will experience a flare after discontinuation of treatment.

Novel therapies are being developed for GCA and PMR. A phase II study investigating the use of abatacept in GCA has been published, with promising results¹⁷⁹. Phase III trials of the IL-6 blocker sarilumab in GCA¹⁸⁰ and PMR¹³⁰ are ongoing; upadacitinib¹⁸¹, a JAK-1 inhibitor, is being tested in a phase III study in GCA, and there are phase II studies of baricitinib¹⁸², mavrilimumab¹⁸³ and secukinumab¹⁸⁴ in GCA. The future of GCA and PMR treatment thus seems promising, and hopefully further novel treatment options will soon be available for improved disease control and reduction of the glucocorticoid burden in these diseases.

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D.C. and C.D. researched data for the article. D.C., E.L.M., F.B. and C.D. wrote the article. All authors made a substantial contribution to discussion of content and reviewed or edited the manuscript before submission.

Competing interests

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