A new era for Giant Cell Arteritis

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Abstract

The landscape of the investigation and management of Giant Cell Arteritis (GCA) is advancing. In this review we will outline the recent advances by searching the current English literature for relevant articles using key words of Giant Cell Arteritis; temporal arteritis; Horton's disease; investigation; and treatment. Delay in diagnosis, diagnostic uncertainty and glucocorticoid (GC) morbidity are among the highest concerns of clinicians and patients in this disease area. The positive news is that fast track pathways, imaging techniques and new therapies are emerging for routine management of GCA. Future directions for intervention in the treatment paradigm will be discussed.

Introduction

Giant cell arteritis (GCA) is a granulomatous medium and large-vessel vasculitis[1]. It is the most common form of systemic vasculitis, with an incidence of between 15 to 25 cases per 100,000 persons over 50 years of age[2]. The incidence of GCA increases with age, almost exclusively affecting people 50 years of age or older[3]. Women account for 65 to 75% of patients; the lifetime risk of GCA in women is 1% compared to 0.5% in men[3,4]. It mainly affects Caucasians and has a higher incidence in Scandinavian countries and in populations of northern European descent[5]. It is rare in Asian and Black Caribbean/ African populations[6,7].

GCA remains a medical emergency because of the risk of sudden irreversible sight loss and stroke. It is a spectrum of phenotypically overlapping conditions including cranial GCA, extra-cranial GCA (otherwise termed large vessel GCA, usually involving the aorta and its larger supra-aortic branches) and polymyalgia rheumatica (PMR)[5,8].The most commonly affected cranial arteries are the temporal, ophthalmic, posterior ciliary and vertebral arteries[9]. 22-83% of newly diagnosed GCA patients have imaging evidence of large vessel-GCA[10].

In clinical practice GCA can be multifaceted: this is due to the seriousness of the condition, diagnostic uncertainty and morbidity associated with treatment. Over the past decade there has been an increased awareness of GCA, leading to an increase in admissions for investigations for suspected GCA[11]. Thus, improved diagnostic pathways, specific tests and targeted management are imperative.

Pathophysiology of Giant Cell Arteritis

GCA mainly affects the medium and large arteries of the external cranial branches of the aorta. The pathological process occurring in GCA is summarised below[2,3,12,13]:

1. Proceeding from an unknown trigger, there is abnormal maturation of vascular dendritic cells (DC) in the adventitia of the large vessel walls. These activated DC recruit and activate cluster differentiation (CD) 4+ naïve T cells.

2. Naïve CD4+ cells are activated and differentiate to T helper (Th) 1 cells, Th17 and T regulatory (Treg) cells.

3. Macrophages within the tunica adventitia of the vessel wall produce IL-6 and IL-1β. Within the tunica media, macrophages secrete metalloproteinases, which degrade the internal elastic lamina and other connective tissue. Reactive oxygen species and secreted IL-6 contribute to inflammation, local vascular damage. Vascular damage and macrophage-derived growth factors such as VEGF and platelet derived growth factor (PDGF) cause intimal hyperplasia and subsequent vascular stenosis and occlusion.

4. In some patients, IFN-γ promotes the differentiation and fusion of highly activated macrophages to form multinucleated giant cells. These giant cells also secrete cytokines and growth factors.

5. The injured arterial cells respond to damage through dysfunctional repair. This leads to media thickening, luminal occlusion, ischaemia and eventually end organ damage.

Genetic influences in GCA

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A genetic component to the development of GCA is supported by evidence of differential prevalence depending on the ethnicity, familial aggregation and multiple genetic associations. GCA has a strong association with the human leukocyte antigen (HLA) region, notably the HLA class II genes[14], which suggests the role of the immune system in its pathophysiology. The number of identified loci remains low, and the reasons for this include the fact that GCA is not common within the general population making it hard to identify susceptibility signals[15]. Two independent signals have been found within the HLA region that are associated with GCA predisposition – one between HLA-DQA1 and HLA-DQA2, and another between HLA-DRA and HLA-DRB1[15].

Non-HLA associations have been associated with an increased risk of GCA, namely PLG (involved in the plasminogen system) and P4HA2 (collagen synthesis); both of these have an important role in neoangiogenesis[16]. Genes encoding proinflammatory cytokines can increase the patient's risk of ischaemic complications, PMR and relapsing disease. The future potential for stratifying the disease, and providing targeted therapy has been posulated[14].

Role of infection in the development of GCA

A potential correlation between onset of GCA and infection is postulated: in analyses infections are found to be more common in GCA patients than non-GCA prior to their diagnosis[17,18]. This leads to a number of theories regarding infection and GCA: namely that infections could be directly responsible for causing GCA from an unregulated inflammatory response, or that the pre-existing immune system

alterations due to the genetic polymorphisms could increase both the risk of infection and development of vasculitis.

In support of the theory that infectious agents trigger GCA specific infectious agents have been found in temporal artery specimens of those diagnosed with GCA, with some then postulating them as a causative factor for the development of GCA. These include herpes simplex virus, chlamydia pneumonia, mycoplasma pneumonia, Epstein-Barr virus, parvovirus B19[19] and varicella zoster virus (VZV)[20]. However, to date no clear conclusions can be drawn, as viruses such as VZV are ubiquitous and the data is currently conflicting.

Seasonal and geographic variation in GCA

Geo-environmental factors have been implicated in the development of GCA and De Smit and colleagues, not only investigated seasonal patterns of temporal artery biopsies (TAB) from Australia and New Zealand, but also summarised the literature[21]. They found that there was no statistically significant relationship between the season of presentation. On analysis of prior studies, they found results to be inconsistent with regard latitude, altitude, solar exposure, socioeconomic status and urban versus rural living again with little conclusion[21].

Disease Associations

PMR is considered by some to be a variant of GCA, where overt vasculitis has either not commenced or is possibly prevented by an unknown inhibiting mechanism[5]. 40 to 60% of patients with GCA also have PMR, conversely 16 to 21% of PMR patients

have GCA – perhaps resulting from sharing of genetic risk factors and pathogenesis[22]. GCA should be considered in PMR patients with marked constitutional symptoms and / or elevated acute phase reactants and where there is an inadequate response to glucocorticoids or relapse[23,24]. PMR typically presents with bilateral shoulder pain and stiffness which is abrupt in onset (usually reaching a peak within two weeks) and worse in the mornings[25]. Other symptoms suggestive of PMR include pelvic girdle aching for more than two weeks, morning stiffness for more than 45 minutes, functional impairment and constitutional symptoms[26]. However, exclusion of a wide range of imitating conditions is also required (e.g. other rheumatological illness such as osteoarthritis or rheumatoid arthritis, drug-induced, endocrine, infective and neoplastic conditions).

Other associations include a significant increased risk of peripheral arterial disease in GCA: the risk ratio among patients with GCA compared with controls was 1.88 (95% CI 1.04-3.41)[27]. Socio-economic deprivation has been reported in GCA, independent of classic cardiovascular risk factors [28]; some consider this evidence that ischaemic complications result predominantly from diagnostic delay [29].

Clinical Presentation – systemic features

Typical clinical features include new-onset headache, scalp tenderness, jaw claudication, fever, fatigue, malaise, anorexia, weight loss and polymyalgia[30]. In most cohorts, new onset headache is typical in about two third of patients, whilst jaw claudication is present in under 50%. Jaw claudication is defined as pain and fatigue in the masseter muscles on protracted or vigorous chewing which eases with rest. It

should not be confused with TMJ dysfunction, dental or gum disease. Tongue claudication is less common, however if present, the likelihood of GCA increases[5]. Headache in GCA can be described as an ache, most commonly over the temporal arteries, but it can occur anywhere over the head. The region over the temporal artery may be sensitive to touch (termed allodynia). Temporal artery abnormalities such as beading (irregular contour), prominence, tenderness with an absent pulse are reported to increase the likelihood ratio for a positive temporal artery biopsy[31] (Figure 1) , although one third of biopsy proven GCA patients have normal temporal arteries on clinical examination.

Constitutional symptoms are present in up to 50% of patients with cranial GCA, including fever, fatigue, night sweats, anorexia and weight loss. These features can be dominant in 15% of patients at first presentation and 20% of patients when relapsing[5]. The fever associated with GCA is usually low grade, but with the potential to reach 39 to 40 degrees centigrade. This is due to a strong systemic acute phase response[32]. Polymyalgic symptoms are the most common extra-cranial manifestation. Peripheral musculoskeletal manifestations are reported in GCA and PMR, including arthritis, swelling of the distal extremities with pitting oedema (more likely PMR than GCA), tenosynovitis and carpal tunnel syndrome[33], although their presence should alert the clinician to possible alternative diagnoses such as rheumatoid arthritis. Due to the wide ranging phenotype, clinicians require a high index of suspicion for GCA[29] because atypical presentations of GCA may delay diagnosis and lead to further complications[34].

The American College of Rheumatology (ACR) classification criteria were created in 1990 (Figure 2). The presence of 3 or more of 5 criteria were associated with a sensitivity of 93.5% and a specificity of 91.2% for GCA when tested in a selected population of patients with vasculitis[35]. The criteria are often mistakenly used for diagnosis, where they function poorly. In the usual clinical setting such as a neuro-ophthalmology or rheumatology clinic they have low sensitivity and poor positive predictive value[36,37]. They have incorrectly labelled GCA as a "headache disease"[24].

Understanding of the wider phenotype of GCA indicates that the ACR 1990 classification criteria require updating: key clinical features of GCA such as constitutional and polymyalgic symptoms, major organ threatening features and newer imaging techniques such as ultrasound, CT, MRI and FDGPET should be included[5].

Other short and long-term complications of GCA include stenosis and large-vessel aneurysms, including thoracic and abdominal aortic aneurysm[38]. Clinically, these can present as intermittent limb claudication, back and chest pain. Rarer complications include stroke, tongue and scalp necrosis[3].

Clinical Presentation – visual features

Visual symptoms can be temporary or permanent. Temporary double vision from cranial nerve palsy occurs in 6-27%. Amaurosis fugax, where there is complete black out of vision for seconds, is a concerning symptom and if disregarded permanent visual loss will occur. Previous visual loss rates, prior to the use of glucocorticoids,

were reported between 30-60%[39]. Currently, vision loss occurs in up to 20% of patients with GCA, most commonly due to arteritic anterior ischaemic optic neuropathy, and in less than 5% due to choroidal infarction, central and branch retinal artery occlusions or posterior ischaemic optic neuropathy[1,40]. Whilst these symptoms can help prevent further ischaemic damage, fewer patients with loss of vision reported preceding symptoms than those without vision loss. Risk factors for visual loss in GCA are older age, male gender, hypertension, a positive temporal artery biopsy and delayed initiation of glucocorticoid[5,41].

Securing a diagnosis

Making a diagnosis of GCA can be difficult due to the non-specific nature of some of the symptoms and a wide range of phenotypes[9]. Diagnosis can be challenging and requires a full history, thorough examination and a combination of investigations. It appears that investigations, along with clinician insight, produces the highest sensitivity and specificity[42].

Serological Investigations

Evidence of an acute phase response is shown through raised erythrocyte sedimentation rate (ESR) or plasma viscosity (PV), and / or c-reactive protein (CRP)[43]. ESR was originally used in the diagnosis of GCA, but a combination of ESR and CRP is being used to give the highest sensitivity and specificity for a diagnosis of GCA. PV is not influenced by age, gender, time to analyse and haematocrit, therefore thought to be better than ESR if available[44]. Thrombocytosis, normocytic normochromic anaemia, with normal white blood cell count or mild leucocytosis can also be

predictive of GCA[45]. Liver transaminases and alkaline phosphatase are often mildly

elevated. A combination of tests have been found to be strong predictors of a

positive diagnosis in those with suspected GCA[43].

Diagnostic uncertainty in GCA presenting to ophthalmology has increased due to the

incorrect assumption of the term "occult GCA". Occult GCA is defined in the

ophthalmology literature as ocular signs without systemic symptoms, but with raised

inflammatory markers[31,46]. In a small percentage of patients, inflammatory markers

may be normal[47]. Whilst inflammatory markers are usually highly elevated in GCA,

lower CRP and/or ESR may be more common in those with visual loss. In 136

patients with biopsy proven GCA from one centre, the ESR and CRP values at

diagnosis were significantly lower in patients with permanent visual loss[48]. In

another multi-centre study of 32 patients with GCA, a low inflammatory response

and the presence of transient cranial ischemic events (such as amaurosis fugax and

double vision) indicated a high risk of developing irreversible ischemic

complications (odds ratio 5, 95% confidence interval 2.05-12.2)[49].

Imaging investigations

Cranial Ultrasound

Vascular ultrasound (US) is used to identify temporal artery oedema, stenosis and

occlusion in GCA[42]. In 10 studies (n=696), the sensitivity has ranged from 55% to

100% and specificity from 78% to 100%. Typically the 'halo sign' is observed, which is

a non-compressible hypoechoic ring around an arterial lumen that represents an

oedematous thickening of the arterial wall due to inflammation[50](Figure 3). A meta-

analysis published in 2010 found a sensitivity of 68% and a specificity of 91% for the unilateral halo sign. The bilateral halo sign was less sensitive, but had a specificity approaching 100%[51]. Ultrasound of the axillary arteries as well as the temporal arteries increases sensitivity of the test[42,52]. Careful clinical evaluation and assessment of the pre-test probability of diagnosis of GCA are still required, because the halo sign can rarely be found in other forms of vasculitis[53]. Further study is also needed to better define the confounding effects of atherosclerosis on temporal and axillary wall thickness[54]. Ultrasonography is cheaper than MRI; it is non-invasive, has rapid access, and allows longitudinal scanning for disease activity; however it requires expertise[42]. The TABUL study investigated cranial ultrasound(US) versus temporal artery biopsy (TAB) and showed the sensitivity of TAB was 39% which was inferior to ultrasound 54%; but the specificity of TAB was 100% which was superior to US at 81%. Further analysis showed that when combined with clinical judgement at two weeks the sensitivity of TAB increased to 91% and the sensitivity of US to 93%, with the specificity of 81% for TAB and 77% for US[42]. A cost saving of £485 was found in favour of US. The sensitivity and specificity of ultrasound in TABUL was lower than the most recent meta-analysis of US use in GCA, where pooled sensitivity was 77% and specificity 96%[55].

Vascular ultrasound is more sensitive to glucocorticoid therapy than TAB. In TABUL, US sensitivity was 64% if performed within one day of starting prednisolone and 47% if performed between 2 and 7 days[42]. Approximately half of positive US findings will be lost within 7 days of steroid treatment[44], although the halo sign may persist for months in some patients[56]. TABUL's ultrasonographers had less scanning experience

than others who have published in this field. Although training and access to US

remain limitations for this technology, this is no reason not to try to develop local

expertise[25]. The EULAR 2018 guidance recommends ultrasound as the first diagnostic

test given adequate expertise and equipment, and if not available TAB[57].

^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET)

^{18}F-FDG-PET is usually combined with low-dose computed tomography (CT) to detect

inflamed vasculature seen in GCA, and this may have a role in assessing disease

activity and extent of involvement (Figure 4)[1]. Although large vessel imaging is

sensitive to glucocorticoid therapy[58], uptake can persist despite treatment and

absence of clinical symptoms in some patients[59]. There are no standardised criteria

for ^{18}F-FDG-PET in large vessel vasculitis but a high proportion of clinicians agree

with the benefits in GCA and diagnostic accuracy[40]. It has shown a sensitivity of 77%

and a specificity of 66%[60]. Whilst use in extracranial involvement of GCA is beneficial,

it cannot be used for cranial GCA due to the proximity of the brain. Another

limitation is in detecting vasculitis of the lower limb due to co-morbid

atherosclerosis which can result in false positive results[61].

Research in other imaging modalities

Research areas in imaging include super high-resolution magnetic resonance imaging

(MRI) of the superficial and extracranial arteries, and transdermal optical coherence

tomography (OCT) of the superficial temporal artery. A contrast-enhanced high-

resolution MRI can demonstrate arterial wall thickening with peri-adventitial and

mural contrast enhancement[1]. Neuroimaging is not usually required for patients

with a typical presentation of GCA, but some patients may have already undergone the investigation previously[34]. Studies have shown MRI to have a sensitivity of 68% to 89% and a specificity of 73% to 97%[1]. Findings that can typically be seen in GCA include non-specific enhancement, enhancement of the optic nerve parenchyma, perineural sheath and optic chiasm. However, these findings are not exclusive to GCA, as they can suggest general orbital inflammatory disease, infiltrating or demyelinating disease. On MRI there can also be T2 hypersensitivity, gadolinium enhancement and diffusion weighted imaging restriction, all of which can be seen in GCA-related anterior ischemic optic neuropathy or posterior ischaemic optic neuropathy[34].

Transdermal Optical Coherence Tomography (OCT) has been reported in a series of eight patients[62]; it demonstrated that transdermal OCT identified the superficial temporal artery. The advantages over TAB were reported to be similar to US and it is quick and easy to use. Currently more research would be required to validate the transdermal OCT utility in GCA.

Histopathological confirmation

A positive TAB gives a definitive diagnosis where a chronic granulomatous inflammation centred on internal elastic lamina is seen. The inflammation can be transmural or patchy comprising of mononuclear lymphohistiocytic cells and occasionally admixed neutrophils and eosinophils.(Figure 5a). Characteristic multi nucleated giant cells (figure 5b) often accompany the inflammatory infiltrates, but these are not required for the diagnosis. Fragmentation and reduplication of the

elastic laminae is usually present (figure 6, 7b).[63] Where timely non-invasive imaging

is unavailable, an early TAB is recommended in all patients where there is suspicion

of GCA[55,64], as over time glucocorticoids will attenuate the histopathological

features. Whilst a positive TAB is specific for GCA, it requires an invasive surgical

procedure. Uncommon procedural risks include facial nerve injury, scalp

ulcer/necrosis, discomfort and surgical wound complications. Stroke has been

reported as an extremely rare complication during the surgery in one individual who

later proved to have an asymptomatic carotid occlusion on the side of the surgery as

the collateral flow had been passing through the biopsied artery[65]. There is a

reported high false negative rate due to segmental involvement[29]. Since these skip

lesions are common, a negative biopsy cannot completely rule out GCA. Deeper

sections throughout the tissue blocks should be made if initial biopsy slides show

only normal artery, and clinical history and examination should be revisited.

Another histologic pattern seen in TAB is the healed pattern, which shows no

inflammation in the arterial wall but can demonstrate discontinuous elastic lamina,

fibrosis of intima/ media and focal calcification (Figure 7a). An elastic stain (EHVG)

highlights significant disruption of the internal elastic lamina with defects extending

over 30-50% of the circumference of the artery (figure 7b[66]). Controversy in the

literature exists around healed arteritis, and this should alert the clinician to re-

examine the history and examination of the patient closely. Additionally,

atherosclerosis can be a confounding finding in TAB, as it causes intimal hyperplasia

and fragmentation of the laminar. Thus, an experienced histopathologist has a

critical role in helping to guide the clinician. The TABUL study[42] suggested significant

variation between pathologists in the interpretation of temporal artery biopsy histology, so consideration should be made to discuss the pathology if the report does not fit the clinical picture.

The British Society for Rheumatology (BSR) recommends that TAB specimens should be no less than 1cm and preferably more than 2cm[67]. Post fixation shrinkage also needs to be taken into consideration[36]. Bilateral primary TAB is common in North America, and increases the yield, but is usually unnecessary[68].

The TABUL study found TAB had a 99% specificity and 39% sensitivity[42]. The sensitivity was much lower than others have reported. In one large cohort of patients with suspected GCA undergoing TAB, the main predictors of a positive biopsy were age at biopsy, referral from ophthalmology, jaw claudication/pain, visual symptoms and raised ESR[9]. In TABUL, TAB sensitivity dropped with glucocorticoid therapy reported from 48% to 33% if performed within 3 days compared to 7 days[42]. The wider literature suggests that there is a 5-10% reduction in positive TAB rate for each week of glucocorticoid treatment[44].

The result of any diagnostic test should be interpreted in light of the pre-test probability. Pre-test probability is estimated by the treating clinician based on the history and examination findings, and all available laboratory results. Various algorithms or clinical prediction rules have been proposed to help with this, but clinical experience remains essential and is why, where possible, all patients with suspected GCA should be referred to a specialist[42].

Other assessments worth considering in GCA

Consider performing a screen for infection including dipstick urinalysis and Chest X-ray (CXR); and a search for mimicking diseases with protein electrophoresis; thyroid function tests; and anti-cytoplasmic neutrophil antibodies (ANCA). Baseline CXR, echocardiogram or large vessel imaging are advocated by some centres to assess for large vessel complications at baseline, in higher risk groups. Occasionally a contrast-enhanced MRI head and orbits may be indicated examining the anterior visual pathways where the cause of an optic neuropathy is not clear.

Determination of pre-existing comorbidities such as hypertension, diabetes mellitus, cataract, cardiovascular disease, peptic ulcer disease, osteoporosis, and glaucoma is important as the treatment can initiate or worsen disease status (Figure 8). Noting co-medication with non-steroidal anti-inflammatory drugs (NSAIDs) and anti-coagulants is important both for immediate and long-term care in GCA.

Management of GCA

GCA is an emergency and many consider that it needs to be treated at the point of a suspected diagnosis due to the threat of sight loss. The principles of management of GCA are to protect vision, to limit other end organ damage and minimise glucocorticoid toxicity and morbidity.

Fast Track Pathways

The mean diagnostic delay for those with cranial symptoms is 9 weeks and 17.6 weeks for patients presenting without cranial symptoms, due to a combination of multiple factors including delayed presentation, delayed clinical suspicion and delayed referral for specialist assessment and confirmatory diagnostic tests[69]. Public awareness of GCA is low and primary care doctors are faced with the often non-specific nature of many early symptoms of GCA and a high prevalence of similar symptoms in the general consulting population[69]. If glucocorticoids are started, but specialist referral is delayed, then the potential for a secure diagnosis is reduced, the clinical signs may have resolved and the diagnostic tests are less likely to be positive with increasing time.

To address these challenges, in certain centres fast-track pathways have been established, providing widely advertised, rapid access to specialist clinical assessment, diagnostic evaluation including vascular ultrasound or other diagnostic tests and immediate therapy. Such pathways have been shown to reduce sight loss and have led to significant cost-savings due to reduction of inpatient care[42] and reduction in TAB rate[42,53]. In one fast track centre, sight loss was reduced from 37 to 9%[41], in another from 27 to 8%[56]. In a third centre, although visual disturbance was equal in the historical and fast track groups, risk of permanent blindness reduced by 88% in the fast track group[70].

Immediate Treatment

Immediate glucocorticoids are the treatment of choice for patients with suspected GCA, however there is uncertainty regarding the optimum dose[1]. Patients who

present to the ophthalmology community with cranial ischaemic symptoms and/or

ophthalmic symptoms are traditionally offered high dose pulse therapy of

glucocorticoid with 0.5-1.0g methylprednisolone for 3-5 days[64,67]. This reduces the

cumulative dose of oral glucocorticoid[1], but there is no evidence that this reduces

rates of sight loss. The current BSR and European League Against Rheumatism

(EULAR) guidelines suggest immediate treatment of GCA using 1mg/kg

glucocorticoid (up to a maximum of 60mg/day) or 40-60mg/day equivalent[64]. This is

to reduce the risk of ischaemic complications, especially to prevent vision loss[64,67].

For those without cranial ischaemic symptoms, an initial dose of 40mg/day is

deemed adequate.

Maintenance therapy

Tapering regimens are empirical. The
BSR guidance recommends a
glucocorticoid taper over about 1-2
years, although this may need to be
adjusted according to response[67].

> **Suggested tapering regime by BSR[67]**
> - 40-60mg prednisolone until symptoms and lab results are normal (2-4 weeks)
> - Reduce dose by 10mg every 2 weeks to 20mg
> - Reduce dose by 2.5mg every 2-4 weeks to 10mg
> - Reduce dose by 1mg every 1-2 months if there is no relapse

Observational cohort studies report relapses in 34-62% of patients, requiring an

increase in glucocorticoid dose, and / or slowing of the tapering regimen[24]. Patients

should be warned to expect treatment for about two years, whilst most patients are

off glucocorticoids at 4-5 years. A small percentage of patients need glucocorticoids

indefinitely[44]. Up to 7% of patients experience recurrent vision loss at 3 years[29,40].

Those who are at high risk of more prolonged glucocorticoid therapy or relapse

include women, those with peripheral arthritis, high initial inflammatory markers

and those with evidence of large vessel involvement[1,71]. Due to the protracted

glucocorticoid burden, there may be significant adverse effects[40].

6% of patients receiving steroid therapy develop serious neuropsychiatric

complications[72]. This effect is dose dependent, with the incidence rapidly rising once

at 40mg/day of steroid[73]. Other adverse effects include the development of a

cushingoid appearance, weight gain and skin atrophy. There are also comorbidities

that can be exacerbated by glucocorticoid therapy, including diabetes, glaucoma and

osteoporosis[1].

Adjunctive therapy in Giant Cell Arteritis

One of the key areas for development in GCA has been to bridge the unmet need for

adjunctive therapy. GCA patients typically exceed a cumulative dose of 5000mg

prednisolone over several years with up to 85% experiencing glucocorticoid related

side effects [Proven]. In the UK alone over 33% had a reported cumulative dose over

10,000mg[74]: the adverse event hazard ratio rising by 3% for every 1000mg

increase[74]. In addition, those with disease refractory to glucocorticoids (Table 1) and

those intolerant or with significant adverse effects from glucocorticoids (Figure: bar

chart of co-morbidities) require adjunctive treatment.

Methotrexate

Methotrexate has been tested as a steroid-sparing agent and in refractory GCA[75-77].

Currently EULAR recommends considering methotrexate in every patient diagnosed

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with GCA, whereas BSR recommends treatment for patients with refractory disease[64,67] based on evidence from three small RCTs[75–77]. A meta-analysis of these trials displays only modest efficacy of 7.5-15mg methotrexate once per week as an adjunct in GCA[78]. Doses of 15-25mg methotrexate weekly, which are conventionally used, have not been formally tested in GCA. The most common adverse effects include gastrointestinal upset, mouth ulcers, temporary hair loss, elevated liver enzymes, leukopenia and teratogenicity[1].

Aspirin

Aspirin is an oral anti-platelet drug, which reduces platelet aggregation, thereby inhibiting thrombosis formation[29]. It also has a wide range of effects on the immune system, inducing tolerance in dendritic cells, inducing Treg and suppressing the transcription of IFN-γ[79,80]. Since glucocorticoids only have marginal effects on IFN-γ, aspirin should theoretically complement their effect in GCA[29]. Due to its antithrombotic action, a small case series of GCA patients have supported its use to reduce the risk of ischaemic events[81]. However, there is a lack of adequate evidence supporting the use of aspirin in GCA, so the clinician must weigh up the potential benefits over potential morbidity[29]. Adverse effects of aspirin include gastrointestinal and cerebral haemorrhage, which will be exacerbated by co-prescription with glucocorticoid.

Cyclophosphamide

In a case series of 35 patients with refractory GCA, 90.3% (n=28) responded to cyclophosphamide with improved disease activity and sustained reduction in

prednisolone dose[82]. A literature review of GCA patients treated with cyclophospahmide[83] showed 84% (n=88) were responsive, alongside other immunosuppressive agents as part of maintenance therapy. However, the rate of side effects was high (33%), and the positive result likely to be affected by reporting bias. The lack of prospective or RCT data and the side effects of cyclophosphamide, especially in this older group of patients, including life threatening infection, limit its use in GCA.

Mycophenolate

There has been one small case series (n=3) suggesting potential of using mycophenolate in GCA[84].

Leflunomide

This inhibits dendritic cell maturation and decreases production of IL-6, TNF, IL-12 and IL-17. It has been shown to have efficacy in Takayasu arteritis and granulomatosis with polyangiitis[85] and is widely used in both psoriatic and rheumatoid arthritis. The most common side effects include diarrhoea, raised blood pressure, elevated liver enzymes and leukopenia. There are case series highlighting its use as a steroid-sparing agent in large vessel vasculitis[85,86]. Adizei 2012[86], showed 22 out of 23 difficult-to-treat GCA patients had either a partial or complete response, as well as a reduced cumulative glucocorticoid dose. Diamantopoulos 2013[85] showed good responses with 11 refractory GCA patients. Recently an open label study comparing Leflunomide as adjunctive therapy to standard care and glucocorticoids alone found that three quarters of the leflunomide group had reduced relapse rate

and decreased cumulative doses of glucocorticoids. Leflunomide needs further high-level evidence to support its use in GCA[87].

Anti-Tumour Necrosis Factor (TNF) Therapy

TAB specimens show TNF in abundance in patients with GCA[88]. The exact role of TNF in the pathogenesis of GCA is still unclear and the role of anti-TNF therapy has not been studied with large sample sizes. Anti-TNF therapies have been considered for use in refractory cases of GCA or corticosteroid dependence, but are not routinely recommended (Table 1)[89].

The new era for GCA: targeted treatment

Tocilizumab

Tocilizumab (TCZ) is a recombinant humanised anti-IL-6 receptor antibody. This competitively inhibits the binding of IL-6 to the membrane bound and soluble IL-6 receptors. IL-6 itself stimulates the release of ESR and CRP from hepatocytes, and promotes the transition from acute to chronic inflammation. Its overproduction contributes to the pathogenesis of GCA[90]. Using drugs that inhibit IL-6 should thereby halt this inflammatory process.

The GiACTA trial[91] investigated the efficacy of 162mg subcutaneous TCZ with a 26-week prednisolone taper, either weekly or every other week. They found that there was a significantly higher rate of sustained remission in the TCZ arms than prednisolone arms (14% in the 26-week prednisolone taper, 18% in the 52-week prednisolone taper 56% in the weekly TCZ arm and 53% in the alternate week TCZ

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arm). The time to first flare was also significantly longer in the TCZ arms. TCZ reduced the cumulative median prednisolone dose by over 40% and perhaps as a result, reported serious adverse events were lower in the TCZ arms.

TCZ has been widely used in rheumatoid arthritis for about ten years and a Cochrane review (n=3334)[92] showed that TCZ was generally well tolerated. However there is a statistically significant association with changes in liver enzymes and total triglycerides and cholesterol[93]. Other adverse drug reactions included gastrointestinal haemorrhage and perforation, infection, headache and hypertension[94]. There is also a risk of injection site reactions when the drug is administered subcutaneously[95]. The risk of tuberculosis (TB) reactivation, malignancy and hepatitis was not found to be significantly elevated[93]. A past medical history of diverticulitis, may be a contraindication for use in GCA, because of the risk of perforation, especially if TCZ is to be used in conjunction with NSAIDs, glucocorticoids or methotrexate[13]. However, at the present time, in the absence of any other effective and approved glucocorticoid sparing agent in GCA, the risk of perforation must be balanced against the risk of ongoing active disease and high dose glucocorticoid use. Studies have shown that there are no differences in the safety profile of TCZ in regards to sex, age, concurrent treatment with NSAIDs, methotrexate and glucocorticoids or mild renal impairment[96]. The safety of TCZ in patients with moderate to severe renal impairment, hepatic impairment or in pregnancy have not yet been studied. Currently, there is a phase 3 clinical trial (ClinicalTrials.gov Identifier: NCT03202368) investigating the long-term safety of subcutaneous TCZ in patients with GCA who have flare or persisting disease activity.

The National Institute for Health and Care Excellence (NICE) and NHS England have approved TCZ for restricted use in GCA[97]. However, it is currently limited to refractory and relapsing disease (Table 1), in those who have not received TCZ previously, and for a maximum of one calendar year of treatment. In the GiACTA trial[40], 17% of the overall cohort were diagnosed with refractory GCA. Within the cohort with refractory GCA, there was a higher prevalence of depression (16% versus 4%), and osteopenia/osteoporosis (33% versus 23%) compared to those without refractory GCA.

Anti-IL-1 Therapy

Ly et al[98] reported the efficacy of Anakinra in 3 patients with refractory GCA, in comparison to conventional treatments. The GiAnT trial (ClinicalTrials.gov Identifier: NCT02902731) is currently in phase 3 looking at 70 patients who will be randomised to two arms: prednisolone plus placebo or prednisolone and 100mg/day anakinra by subcutaneous injection. The study is expected to be completed by March 2022.

Anti-T Cell Therapy

Langford et al, 2017[99] (n=49), supported the use of abatacept as it showed a significantly higher rate of relapse-free survival to standard glucocorticoid therapy and it was not associated with a higher rate of toxicity. A clinical trial (ClinicalTrial.gov Identifier: 00556439) is currently underway looking at abatacept for treating adults with GCA and Takayasu's arteritis.

Conclusion

GCA remains a disease that causes concern for clinicians and patients either in diagnosis or in suspected relapse. Wider access and validation of imaging techniques, not only for diagnosis but longitudinal monitoring, is underway. We are now embarking on the era of targeted treatment for GCA, with many avenues to pursue. Patients will benefit from fast track pathways where close partnership with other teams that care for those with GCA including rheumatology, medicine, neurology and primary care, will facilitate early diagnosis and improve long term management.

Contributor Statement

Lyons H: literature review; drafting of the manuscript and figures.

Quick V: Rheumatology expert in GCA; drafting and critical review of the manuscript.

Provision of the imaging figures.

Sinclair AJ: Neurology expert in headache; critical review of the manuscript.

Nagaraju S: Neurohistopathologist; critical review of the manuscript and provision of

the histopathology images.

Mollan SP: concept and design of the review; critical review of the manuscript.

All authors have read and approved the final manuscript.

References

1. Buttgereit F, Dejaco C, Matteson E, Dasgupta B. Polymyalgia Rheumatica and Giant Cell Arteritis: A Systematic Review. JAMA. 2016;315(22):2442–58.

2. Weyand CM, Goronzy JJ. Medium- and Large-Vessel Vasculitis. N Engl J Med. 2003;349(2):160–9.

3. Weyand CM, Goronzy JJ. Giant-Cell Arteritis and Polymyalgia Rheumatica. N Engl J Med. 2014;371(1):50–7.

4. Crowson CS, Matteson EL, Myasoedova E, Michet CJ, Ernste FC, Warrington KJ, et al. The Lifetime Risk of Adult-Onset Rheumatoid Arthritis and Other Inflammatory Autoimmune Rheumatic Diseases. Arthritis Rheum. 2011;63(3):633–9.

5. Dejaco C, Duftner C, Buttgereit F, Matteson EL, Dasgupta B. The spectrum of giant cell arteritis and polymyalgia rheumatica: revisiting the concept of the disease. Rheumatol. 2017;56(4):506–15.

6. Smith C, Fidler W, Pinals R. The epidemiology of giant cell arteritis: report of a ten-year study in Shelby County, Tennessee. Arthritis Rheum. 1983;26:1214–9.

7. Wigley R, Zhang N, Zeng Q, Shi C, Hu D, Couchman K, et al. Rheumatic diseases in China: ILAR-China study comparing the prevalence of rheumatic symptoms in northern and southern rural populations. J Rheumatol. 1994;21:1484–90.

8. Koster M, Matteson E, Warrington KJ. Large-vessel GCA: diagnosis, monitoring and management. Rheumatology. 2018;57(2):32–42.

9. Gajree S, Borooah S, Dhillon N, Goudie C, Smith C, Aspinall P. Temporal Artery Biopsies in South East Scotland : A Five Year Review. J R Coll Physicians Edinb. 2017;47(2):124–8.

10. Kermani T, Warrington KJ, Crowson CS, Ytterberg SR, Hunder GG, Gabriel SE, et al. Large-Vessel Involvement in Giant Cell Arteritis: A Population-Based Cohort Study of the Incidence-Trends and Prognosis. Ann Rheum Dis. 2013;72(12):1989–94.

11. Mollan SP, Begaj I, Mackie S, O'Sullivan EP, Denniston AK. Increase in admissions related to giant cell arteritis and polymyalgia rheumatica in the UK, 2002-13, without a decrease in associated sight loss: Potential implications for service provision. Rheumatol (United Kingdom). 2015;54(2):375–7.

12. Al-Mousawi AZ, Gurney SP, Lorenzi AR, Pohl U, Dayan M, Mollan SP. Reviewing the pathophysiology behind the advances in the management of Giant Cell Arteritis. Ophthalmol Ther. 2019 in progress

13. Mollan SP, Horsburgh J. Profile of tocilizumab and its potential in the treatment of giant cell arteritis. Eye Brain. 2018;10:1–11.

14. Carmona F, Martín J, Gonzalez-Gay MA. New insights into the pathogenesis of giant cell arteritis and hopes for the clinic. Expert Rev Clin Immunol. 2016;12(1):57–66.

15. Ortiz-Fernández, L, Carmona, FD, López-Mejías, R et al. Cross-phenotype analysis of Immunochip data identifies KDM4C as a relevant locus for the development of systemic vasculitis. Annals of the Rheumatic Diseases 2018; 77 (4):589-595.

16. Carmona F, Vaglio A, Mackie S, Hernández-Rodríguez J, Monach PA, Castañeda S, et al. A Genome-wide Association Study Identifies Risk Alleles in Plasminogen and P4HA2 Associated with Giant Cell Arteritis. Am J Hum Genet. 100(1):64–74.

17. Russo M, Waxman J, Abdo A, Serebro L. Correlation Between Infection and the Onset of the Giant-Cell (Temporal) Arteritis Syndrome - a Trigger Mechanism. Arthritis Rheum. 1995;38(3):374–80.

18. Brault C, Riis AH, Mor A, Duhaut P, Thomsen RW. Does low risk of infections as a marker of effective immunity predict increased risk of subsequent giant cell arteritis or polymyalgia rheumatica? A Danish population-based case-control study. *Clin Epidemiol*. 2018;10:1533-1543.

19. Álvarez-Lafuente R, Fernández-Gutiérrez B, Jover JA, Júdez E, Loza E, Clemente D, et al. Human parvovirus B19, varicella zoster virus, and human herpes virus 6 in temporal artery biopsy specimens of patients with giant cell arteritis: analysis with quantitative real time polymerase chain reaction. Ann Rheum Dis. 2005;64(5):780–2.

20. Procop GW, Eng C, Clifford A, et al. Varicella Zoster Virus and Large Vessel Vasculitis, the Absence of an Association. *Pathog Immun*. 2017;2(2):228-238

21. De Smit E, Clarke L, Sanfilippo PG, et al. Geo-epidemiology of temporal artery biopsy-positive giant cell arteritis in Australia and New Zealand: is there a seasonal influence?. *RMD Open*. 2017;3(2):e000531. Published 2017 Aug 29. doi:10.1136/rmdopen-2017-000531

22. Gonzalez-Gay MA. Giant cell arteritis and polymyalgia rheumatica: two different but often overlapping conditions. Semin Arthritis Rheum. 2018;33(5):289–93.

23. Dejaco C, Singh YP, Perel P, Hutchings A, Camellino D, Mackie S, et al. 2015 Recommendations for the Management of Polymyalgia Rheumatica A European League Against Rheumatism / American College of Rheumatology Collaborative Initiative. Arthritis Rheumatol. 2015;67(10):2569–80.

24. Dejaco C, Brouwer E, Mason J, Buttgereit F, Matteson EL, Dasgupta B. Giant cell arteritis and polymyalgia rheumatica: current challenges and opportunities. Nat Rev Rheumatol. 2017;13(10):578–92.

25. Quick V, Kirwan J. Our approach to the diagnosis and treatment of polymyalgia rheumatica and giant cell (temporal) arteritis. J R Coll Physicians Edinb. 2012;42:341–9.

26. González-Gay MA, Matteson EL, Castañeda S. Polymyalgia rheumatica. Lancet. 2018;390(10103):1700–12.

27. Ungprasert P, Thongprayoon C, Srivali N, Cheungpasitporn W. Peripheral arterial disease in patients with giant cell arteritis : a meta-analysis. Int J Rheum Dis. 2016;19(8):819–25.

28. Mackie S, Dasgupta B, Hordon L, Gough A, Green M, Hollywood J, et al. Ischaemic manifestations in giant cell arteritis are associated with area level socio- economic deprivation, but not cardiovascular risk factors. Rheumatology. 2011;50(11):2014–22.

29. Mollan S, Sharrack N, Burdon M, Denniston A. Aspirin as adjunctive treatment for giant cell arteritis. Cochrane Database Syst Rev. 2014;(8).

30.   Hunder G. Clinical features of GCA/PMR. Clin Exp Rheumatol. 2000;18(4):6–8.

31.   Smetana G, Shmerling R. Does this patient have temporal arteritis? JAMA. 287(1):92–101.

32.   Salvarani C, Cantini F, Boiardi L, Hunder G. Polymyalgia Rheumatica and Giant-Cell Arteritis. N Engl J Med. 2002;347(4):261–71.

33.   Salvarani C, Hunder G. Musculoskeletal manifestations in a population-based cohort of patients with giant cell arteritis. Arthritis Rheumatol. 1999;42(6):1259–66.

34.   D'Souza NM, Morgan ML, Almarzouqi SJ, Lee AG. Magnetic resonance imaging findings in giant cell arteritis. Eye. 2016;(January):1–5.

35.   Hunder GG, Bloch D, Michel B, Stevens M, Arend W, Calabrese L, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. Arthritis Rheum. 1990;33(8):1122–8.

36.   Murchison A, Gilbert M, Bilyk J, Eagle R, Pueyo V, Sergott R, et al. Validity of the American College of Rheumatology Criteria for the Diagnosis of Giant Cell Arteritis. Am J Ophthalmol. 2012;154(4):722–9.

37.   Rao J, Allen N, Pincus T. Limitations of the 1990 ACR rheumatology classification criteria in the diagnosis of vasculitis. Ann Intern Med. 1998;129(5):345–52.

38.   Evans J, O'Fallon W, Hunder G. Increased Incidence of Aortic Aneurysm and Dissection in Giant Cell (Temporal) Arteritis: A Population-Based Study. Ann Intern Med. 1995;122:502–7.

39.   Birkhead N, Wagener H, Shick R. Treatment of temporal arteritis with adrenal corticosteroids; results in fifty-five cases in which lesion was proved at biopsy. J Am Med Assoc. 1957;163(10):821–7.

40.   Tuckwell K, Collinson N, Dimonaco S, Klearman M, Blockmans D, Brouwer E, et al. Newly-Diagnosed Versus Relapsing Giant Cell Arteritis: Baseline data from the GiACTA trial. Semin Arthritis Rheum. 2017;46(5):657–64.

41.   Patil P, Williams M, Maw W, Achilleos K, Elsideeg S, Dejaco C, et al. Fast track pathway reduces sight loss in giant cell arteritis: results of a longitudinal observational cohort study. Clin Exp Rheumatol. 2015;33:103–6.

42.   Luqmani R, Lee E, Singh S, Gillett M, Schmidt W, Bradburn M, et al. The Role of Ultrasound Compared to Biopsy of Temporal Arteries in the Diagnosis and Treatment of Giant Cell Arteritis (TABUL): a diagnostic accuracy and cost-effectiveness study. Heal Technol Assess. 2016;20(90):1–238.

43.   Ing E, Lahaie L, Toren A, Ing R, Chen J, Arora N, et al. Multivariable prediction model for suspected giant cell arteritis: development and validation. Clin Ophthalmol. 2017;11:2031–42.

44.   Quick V, Kirwan J. In: David S Younger (ed) The Vasculitidies, General Considerations and Systemic Vasculitis Vol.1. New York: Nova Science. 2015. Chapter 17. p311-336.

45.   Foroozan R, Danesh-Meyer H, Savino P, Gamble G, Mekari-Sabbagh O, Sergott R. Thrombocytosis in patients with biopsy-proven giant cell arteritis. Ophthalmology. 2002;109(7):1267–71.

46.   Cullen J. Occult temporal arteritis. Trans Ophthalmol Soc UK. 1963;83:725–36.

47.   Yu-Wai-Man P, Dayan M. Giant cell arteritis with normal inflammatory markers. Acta Ophthalmol Scand. 2007;85(4):460.

48.   Salvarani C, Cimino L, Macchioni P, Consonni D, Cantini F, Bajocchi G, et al. Risk factors for visual loss in an Italian population-based cohort of patients with giant cell arteritis. Arthritis Rheum. 2005;53(2):293–7.

49.   Cid M, Font C, Oristrell J, de la Sierra A, Coll-Vinent B, Lopez-Soto A, et al. Association between strong inflammatory response and low risk of developing visual loss and other cranial ischemic complications in giant cell (temporal) arteritis. Arthritis Rheum. 1998;41(1):26–32.

50.   Schafer V, Chrysidis S, Dejaco C, Duftner C, Lagnocco A, Bruyn G, et al. Assessing Vasculitis in Giant Cell Arteritis by Ultrasound: Results of OMERACT Patient-based Reliability Exercises. J Rheumatol. 2018;45(7).

51.   Arida A, Kyprianou M, Kanakis M, Sfikakis PP. The diagnostic value of ultrasonography-derived edema of the temporal artery wall in giant cell arteritis: a second meta-analysis. BMC Musculoskelet Disord. 2010;11:44.

52.   Schmidt W, Seifert A, Gromnica-Ihle E, Krause A, Natusch A. Ultrasound of proximal upper extremity arteries to increase the diagnostic yield in large-vessel giant cell arteritis. Rheumatol. 2008;47(1):96–101.

53.   Monti S, Floris A, Ponte C, Schmidt W, Diamantopoulos A, Pereira C, et al. The use of ultrasound to assess giant cell arteritis: review of the current evidence and practical guide for the rheumatologist. Rheumatol. 2018;57(2):227–35.

54.   Sammel A, Hamilton D, Omari A, McGrath M. Comment on: The proposed role of ultrasound in the management of giant cell arteritis in routine clinical practice. Rheumatology. 2018;57(6):1124–5.

55.   Duftner C, Dejaco C, Sepriano A, Falzon L, Schmidt W, Ramiro S. Imaging in diagnosis, outcome prediction and monitoring of large vessel vasculitis: a systematic literature review and meta-analysis informing the EULAR recommendations. RMD Open. 2018;4(1).

56.   Schmidt W. Ultrasound in the diagnosis and management of giant cell arteritis. Rheumatology. 2018;57(2):22–31.

57.   Dejaco C, Ramiro S, Duftner C, Besson F, Bley T, Blockmans D, et al. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. Ann Rheum Dis. 2018;77(5):636–43.

58.   Hauenstein C, Reinhard M, Geiger J, Markl M, Hetzel A, Treszl A, et al. Effects of early corticosteroid treatment on magnetic resonance imaging and ultrasonography findings in giant cell arteritis. Rheumatol. 2012;51(11):1999–2003.

59.   Blockmans D, de Ceuninck L, Vanderschueren S, Knockaert D, Mortelmans L, Bobbaers H. Repetitive 18F-fluorodeoxyglucose positron emission tomography in giant cell arteritis: a prospective study of 35 patients. Arthritis Rheum. 2006;55(1):131–7.

60.   Blockmans D, Stroobants S, Maes A, Mortelmans L. Positron emission tomography in giant cell arteritis and polymyalgia rheumatica: evidence for inflammation of the aortic arch. Am J Med. 2018;108(3):246–9.

61.   Förster S, Tato F, Weiss M, Czihal M, Rominger A, Bartenstein P, et al. Patterns of extracranial involvement in newly diagnosed giant cell arteritis assessed by physical examination, colour coded duplex sonography and FDG-PET. Vasa. 2011;40(3):219–27.

62.   Mollan S, Keane P, Denniston A. The use of transdermal optical coherence

tomography to image the superficial temporal arteries. Eye. 2017;31(1):157–60.

63.   Nesher G. The diagnosis and classification of giant cell arteritis. J Autoimmun. 2014;48–49:73–5.

64.   Mukhtyar C, Guillevin L, Cid MC, Dasgupta B, de Groot K, Gross W, et al. EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis. 2009;68(3):318–23.

65.   Schlezinger NS, Schatz NJ: Giant cell arteritis (temporal arteritis). Trans Am Neurol Assoc. 1971; 96: 12–15

66.   Allsop C, Gallagher P. Temporal artery biopsy in giant-cell arteritis. A reappraisal. Am J Surg Pathol. 1981;5(4):317–23.

67.   Dasgupta B, Borg FA, Hassan N, Alexander L, Barraclough K, Bourke B, et al. Guidelines BSR and BHPR guidelines for the management of giant cell arteritis. Rheumatol. 2010;49(8):1594–7.

68.   Boyev L, Miller N, Green W. Efficacy of unilateral versus bilateral temporal artery biopsies for the diagnosis of giant cell arteritis. Am J Ophthalmol. 1999;128(2):211–5.

69.   Prior J, Ranjbar H, Belcher J, Mackie S, Helliwell T. Diagnostic delay for giant cell arteritis - a systematic review and meta-analysis. BMC Med. 2017;15(120).

70.   Diamantopoulos A, Haugeberg G, Lindland A, Myklebust G. The fast-track ultrasound clinic for early diagnosis of giant cell arteritis significantly reduces permanent visual impairment: towards a more effective strategy to improve clinical outcome in giant cell arteritis? Rheumatol. 2016;55(1):66–70.

71.   Blockmans S, Coudyzer W, Vanderschueren S, Stroobants S, Loeckx D, Heye S, et al. Relationship between fluorodeoxyglucose uptake in the large vessels and late aortic diameter in giant cell arteritis. Rheumatol. 2008;47(8):1179–84.

72.   Dubovsky A, Arvikar S, Stern T, Axelrod L. The neuropsychiatric complications of glucocorticoid use: steroid psychosis revisited. Psychosomatics. 2012;53(2):103–15.

73.   West S, Kenedi C. Strategies to prevent the neuropsychiatric side-effects of corticosteroids: a case report and review of the literature. Curr Opin Organ Transpl. 2014;19(2):201–8.

74.   Broder M, Sarsour K, Chang E, Collinson N, Tuckwell K, Napalkov P, et al. Corticosteroid-related adverse events in patients with giant cell arteritis: A claims-based analysis. Semin Arthritis Rheum. 2016;46(2):246–52.

75.   Spiera R, Mitnick H, Kupersmith M, Richmond M, Spiera H, Peterson M, et al. A prospective, double-blind, randomized, placebo controlled trial of methotrexate in the treatment of giant cell arteritis (GCA). Clin Exp Rheumatol. 2001;19(5):495–501.

76.   Hoffman GS, Cid MC, Hellmann DB, Guillevin L, Stone JH, Schousboe J, et al. A multicenter, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis. Arthritis Rheum. 2002;46(5):1309–18.

77.   Jover JA, Hernández-García C, Morado I, Vargas E, Banares A, Fernández-Gutiérrez B. Combined treatment of giant-cell arteritis with methotrexate and prednisone. a randomized, double-blind, placebo-controlled trial. Ann Intern

Med. 2001;134(2):106–14.

78. Mahr A, Jover J, Spiera R, Hernández-García C, Fernández-Gutiérrez B, Lavalley M, et al. Adjunctive Methotrexate for Treatment of Giant Cell Arteritis. Arthritis Rheum. 2007;56(8):2789–97.

79. Hussain M, Javeed A, Ashraf M, Zhao Y, Mukhtar MM, Rehman MU. Aspirin and immune system. Int Immunopharmacol. 2012;12(1):10–20.

80. Weyand CM, Kaiser M, Yang H, Younge B, Goronzy JJ. Therapeutic effects of acetylsalicylic acid in giant cell arteritis. Arthritis Rheum. 2002;46(2):457–66.

81. Rüegg S, Engelte S, Jeanneret C, Hetzel A, Probst A, Steck A, et al. Bilateral vertebral artery occlusion resulting from giant cell arteritis: report of 3 cases and review of the literature. Med. 2003;82(1):1–12.

82. Loock J, Henes J, Kotter I, Witte T, Lamprecht P, Schirmer M, et al. Treatment of refractory giant cell arteritis with cyclophosphamide: a retrospective analysis of 35 patients from three centres. Clin Exp Rheumatol. 2012;30((1 suppl 70)):70–6.

83. de Boysson H, Boutemy J, Creveuil C, Ollivier Y, Letellier P, Pagnoux C, et al. Is there a place for cyclophosphamide in the treatment of giant-cell arteritis? A case series and systematic review. Semin Arthritis Rheum. 2013;43(1):105.

84. Sciascia S, Piras D, Baldovino S, Russo A, Naretto C, Rossi D, et al. Mycophenolate mofetil as steroid-sparing treatment for elderly patients with giant cell arteritis: report of three cases. Aging Clin Exp Res. 2012;24(3):273–7.

85. Diamantopoulos AP, Hetland H, Myklebust G. Leflunomide as a corticosteroid-sparing agent in giant cell arteritis (GCA) and polymyalgia rheumatica (PMR): A consecutive case series. Biomed Res Int. 2013;

86. Adizie T, Christidis D, Dharmapaliah C, Borg F, Dasgupta B. Efficacy and tolerability of leflunomide in difficult-to-treat polymyalgia rheumatica and giant cell arteritis: a case series. Int J Clin Pr. 2012;66(9):906–9.

87. Hočevar A, Ješe R, Rotar Z, Tomšič M. Does leflunomide have a role in giant cell arteritis? An open-label study. Clin Rheumatol. 2018;1–6.

88. Martínez-Taboada VM, Rodríguez-Valverde V, Carreño L, López-Longo J, Figueroa M, Belzunegui J, et al. A double-blind placebo controlled trial of etanercept in patients with giant cell arteritis and corticosteroid side effects. Ann Rheum Dis. 2008;67(5):625–30.

89. Seror R, Baron G, Hachulla E, Debandt M, Larroche C, Puéchal X, et al. Adalimumab for steroid sparing in patients with giant-cell arteritis: Results of a multicentre randomised controlled trial. Ann Rheum Dis. 2014;73(12):2074–81.

90. Korn T, Mitsdoerffer M, Croxford AL, Awasthi A, Dardalhon VA, Galileos G, et al. IL-6 controls Th17 immunity in vivo by inhibiting the conversion of conventional T cells into Foxp3+ regulatory T cells. Proc Natl Acad Sci. 2008;105(47):18460–5.

91. Stone JH, Tuckwell K, Dimonaco S, Klearman M, Aringer M, Blockmans D, et al. Trial of Tocilizumab in Giant-Cell Arteritis. N Engl J Med. 2017;377(4):317–28.

92. Singh J, Beg S, Lopez-Olivo M. Tocilizumab for Rheumatoid Arthritis: A Cochrane Systematic Review. J Rheumatol. 2011;38(1):10–20.

93. Genovese M, McKay J, Nasonov E, Mysler E, da Silva N, Alecock E, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in

rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: The tocilizumab in combination with traditional disease-modifying antirheumatic drug the. Arthritis Rheum. 2008;58(10):2968–80.

94. Jones G, Sebba A, Gu J, Lowenstein MB, Calvo A, Gomez-Reino JJ, et al. Comparison of tocilizumab monotherapy versus methotrexate monotherapy in patients with moderate to severe rheumatoid arthritis: the AMBITION study. Ann Rheum Dis. 2010;69(01):88–96.

95. Burmester GR, Rubbert-Roth A, Cantagrel A, Hall S, Leszczynski P, Feldman D, et al. Efficacy and safety of subcutaneous tocilizumab versus intravenous tocilizumab in combination with traditional DMARDs in patients with RA at week 97 (SUMMACTA). Ann Rheum Dis. 2016;75(1):68 LP-74.

96. Sheppard M, Laskou F, Stapleton PP, Hadavi S, Dasgupta B. Tocilizumab (Actemra). Hum Vaccin Immunother. 2017;13(9):1972–88.

97. National Institute for Health and Care Excellence. Tocilizumab for treating giant cell arteritis [Internet]. NICE technology appraisal guidance TA518. 2018 [cited 2018 Sep 7]. Available from: https://www.nice.org.uk/guidance/ta518

98. Ly KH, Stirnemann JÔ, Liozon E, Michel M, Fain O, Fauchais AL. Interleukin-1 blockade in refractory giant cell arteritis. Jt Bone Spine. 2014;81(1):76–8.

99. Langford CA, Cuthbertson D, Ytterberg SR, Khalidi N, Monach PA, Carette S, et al. A Randomized, Double-Blind Trial of Abatacept (CTLA-4Ig) for the Treatment of Giant Cell Arteritis. Arthritis Rheumatol. 2017;69(4):837–45.

100. Vodopivec I, Rizzo J. Ophthalmic manifestations of giant cell arteritis. Rheumatology. 2018;57(2):63–72.

101. Calvo-Romero J. Giant cell arteritis. Postgr Med J. 2003;79(935):511–5.

102. De Silva M, Hazleman BL. Azathioprine in giant cell arteritis/polymyalgia rheumatica: a double-blind study. Ann Rheum Dis. 1986;45(2):136–8.

103. Schaufelberger C, Möllby H, Uddhammar A, Bratt J, Nordborg E. No additional steroid-sparing effect of cyclosporine A in giant cell arteritis. Scand J Rheumatol. 2006;35(4):327–9.

104. Liozon F, Vidal E, Barrier J. Dapsone in giant cell arteritis treatment. Eur J InternMed. 1993;4:207–14.

105. Hoffman GS, Cid MC, Rendt-Zagar K, Merkel P, Weyand C, Stone J, et al. Infliximab for maintenance of glucocorticosteroid-induced remission of giant cell arteritis: a randomized trial. Ann Intern Med. 2007;146(9):621–30.

106. Coath F, Gillbert K, Griffiths B, Hall F, Kay L, Lanyon P, et al. Giant cell arteritis: new concepts, treatments and the unmet need that remains. Rheumatology (Oxford). 2018 Nov 12.

Figure Legends

Figure 1: Prominent, beaded, pulseless, tender temporal artery in a patient with

biopsy proven giant cell arteritis. Abnormality detected by patient three weeks prior

to new onset temporary, then permanent double vision, followed by anterior ischaemic optic neuropathy and complete loss of vision to perception of light.

Figure 2: Diagram of frequency of symptoms of GCA and the American College of Rheumatology (ACR) 1990 criteria for the definite diagnosis of GCA[30,100,101].

Figure 3: These are Temporal Artery Ultrasound images showing (A) longitudinal and (B) cross sectional images of a normal artery; (C) longitudinal and (D) cross section image of the non-compressible, hypoechoic "halo sign" (white asterisks).

Figure 4: A 67 year old Caucasian lady presented with headache, PMR, drenching night sweats, weight loss and CRP 120. ^{18}FDG PET-CT fused images show^{18}FDG avid large vessel GCA (white arrows) of the thoracic aorta in sagittal (A), coronal (B) and transverse view (C). Inflammatory activity extends into the subclavian and common carotid arteries (D).

Figure 5: Key histopathological features of GCA. (A) H&E x 100, superficial temporal artery with marked intimal thickening. (B) Thick arrow head denotes inflammatory cells in the media and adventitia.

Figure 6: Key histopathological feature of GCA with EHVG stain x 200 thick arrow head points to fragments of internal elastic laminae remaining and duplication.

Figure 7: Key histopathological feature of healed arteritis. (A) thick arrow head shows calcification at the intima media border and (B) an elastic stain (EHVG) highlights significant disruption of the internal elastic lamina with defects extending over 30-50% of the circumference of the artery.

Figure 8: Common co-morbidities and adverse effects of glucocorticoids as adapted from Tuckwell *et al*.

Tables

Table 1: Current definitions of disease state, as adapted from Dasgupta et al, 2018[106]

Terminology	Definition
Relapse	Recurrence of signs or symptoms of GCA attributable to GCA as determined by the clinician and necessitating an increase in treatment in a GCA patient who has previously responded to treatment.
Refractory	Those who never achieve remission, regardless of treatment with a course of glucocorticoids, which would be considered adequate to induce remission. Lower dose regimens may constitute optimal care if the maximum safe dose of glucocorticoid must be exceeded in order to control disease e.g. in glucocorticoid induced psychiatric disturbance, pancreatitis, or uncontrolled diabetes or hypertension.
Remission	Absence of signs or symptoms of GCA.
Sustained remission	Sustained absence of signs or symptoms of GCA.

Table 2: Therapies not routinely recommended for GCA.

Drug	Efficacy in GCA
Azathioprine	In a double-blind study of 31 patients with PMR and GCA, azathioprine 100-150mg/day appeared to reduce the overall cumulative dose of glucocorticoid. However, there was a higher discontinuation rate compared to placebo, most likely due to less

	tolerable adverse effects and so this trial cannot be interpreted[102].
Cyclosporine	Cyclosporine A showed no clinical efficacy and carried the risk of hypertension and creatinine increment[103].
Dapsone	Dapsone showed a moderate efficacy. Its side effect profile inhibits routine use with increasing the risk of anaemia, agranulocytosis and a rash[104].
Sirukumab	This is an IL- inhibitor. The SIRRESTA study (ClinicalTrials.gov Identifier: NCT02531633) was designed to evaluate the efficacy and safety of this drug in GCA, however it was terminated due to a change of rights and its discontinued development in GCA.
Infliximab	Infliximab was reported to be ineffective in Hoffman et al, 2007[105] (n=44) as it failed to improve the rate of remission or reduce glucocorticoid requirement. 25% developed antibodies against Infliximab 20 weeks after administration of the last dose.
Adalimumab	The HECTHOR trial[89] (n=70) reported that 10-week's treatment with adalimumab was not associated with a lower rate of relapse or a glucocorticoid-sparing effect.
Etanercept	Martínez-Taboada et al, 2008[88] (n=17) etanercept was reported to have a lower number of relapses, although not statistically significant, and a significantly lower overall cumulative prednisolone dose. They could not draw definitive conclusions due to the small study sample.

Summary points:

What was known before

1. TAB was the "gold standard" for diagnosis of GCA.

2. Serum IL-6 was found to be elevated in those with active GCA.

3. The only effective treatment was with high dose glucocorticoids, which have a significant cumulative morbidity in this population.

What is known now

1. Tests including non-invasive imaging in conjunction with clinical expertise are the current gold standard for diagnosis of GCA.

2. Fast track pathways reduce GCA related morbidity, such as visual loss; reduce the potential for over treatment in those with suspected in GCA and are cost effective.

3. Tocilizumab, an IL-6 inhibitor, is licenced for treatment of all GCA patients. In Scotland, Wales and Northern Ireland it is funded for all GCA patients. In England it funded for refractory GCA for up to one year of treatment.