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Giant Cell Arteritis 2

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This is the second in a Series of two papers about giant cell arteritis

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For years, clinicians and researchers working on giant cell arteritis have been battling with the conundrum of a disease that displays a short-term steroid responsiveness but is burdened by a remarkable risk of flares and chronic damage in the long term. This issue should be addressed by a change in the direction of research and clinical practice. Evidence suggests that giant cell arteritis is not a monolithic disease; it varies in extent and severity. Hence, treatment should be guided by disease stratification. The current one-size-fits-all strategy leads to overreliance on glucocorticoids and progression of glucocorticoid-related and disease-related complications. A new approach requires disease stratification using clinical, laboratory, histology, and imaging parameters. A giant cell arteritis registry might offer opportunities to scrutinise disease course and prognostic variables early; however, more studies that directly incorporate disease stratification through the above parameters are required. This Series paper also suggests that future clinical trials should be targeted at patients with different disease strata of giant cell arteritis and should incorporate ultrasound, PET-CT scanning, and other imaging modalities as key outcomes.

Introduction

Giant cell arteritis is commonly misunderstood by the medical community as a headache disease of older people that responds easily to glucocorticoids. This view of giant cell arteritis as a primary care-managed disease that is easy to diagnose and treat has reduced rheumatologists' interest in favour of supposedly fascinating and complex autoimmune diseases, such as systemic lupus erythematosus, or inflammatory conditions with more therapeutic choices, such as rheumatoid arthritis. Emerging evidence suggests that this simplistic misconception of giant cell arteritis needs to be jettisoned.

Giant cell arteritis is not just a cranial disease affecting temporal arteries but also a critically ischaemic disease[1] and a systemic inflammatory disorder, with many patients showing involvement of the aorta and its branches.[2] An approach to giant cell arteritis based on clinical evaluation with occasional histological confirmation should, therefore, be replaced by a fast-track imaging-based comprehensive diagnostic process.[3]

Although glucocorticoids play a pivotal role in controlling the initial inflammation, they are unable to fully extinguish disease activity and halt long-term vascular remodelling and damage. There are two main pathogenetic pathways in giant cell arteritis: one is mediated by T-helper-1 [Th1] cells and the other by Th17 cells. Glucocorticoids have little direct effect on inhibiting Th1-mediated arterial injury.[4] Long-term glucocorticoid use in such a vulnerable population is also associated with serious adverse events and irreversible complications,[5] which leads to the paradoxical situation of a disease regarded in the short term as steroid-responsive, but with longer-term damage related both to the disease itself and its treatment. Hence, it is imperative to limit glucocorticoids to minimum effective doses and duration; to focus on early disease stratification; to concentrate on long-term outcomes and damage; and to promote effective and safe new steroid-sparing agents.

Critical outcomes

One of the main factors contributing to the perception of giant cell arteritis as an easy-to-treat disease is the excellent response to high-dose glucocorticoids in almost all patients.[6] Once glucocorticoids are started, it takes a few days for most of the symptoms to disappear and for laboratory inflammatory markers to decrease. For these reasons, when a prompt and satisfying improvement is not observed, a diagnosis of giant cell arteritis should be questioned.[7]

However, the critical phase to evaluate the response of patients with giant cell arteritis is not at the start of therapy but after dose reduction, particularly when the dose is decreased to less than 10 mg daily of prednisolone-equivalent.[8] Disease activity at low doses tells clinicians whether the disease is truly controlled or clinically quiescent yet suppressed by glucocorticoids. In addition to flares, giant cell arteritis is also burdened with large vessel complications, including stenosis, aneurysms, and dissections.[9] Therefore, the real challenge of giant cell arteritis is not to extinguish the acute inflammatory process, but to provide long-term, safe prevention of disease relapses and incipient damage. However, not all patients with giant cell arteritis have relapsing disease. The frequency of relapses is reported to reach 86% in those treated with glucocorticoid monotherapy and 44% when the interleukin (IL)-6 receptor antagonist tocilizumab is added.[10] Similarly, not all patients end up developing vascular damage. For these reasons, baseline stratification according to the risk of complications is needed.

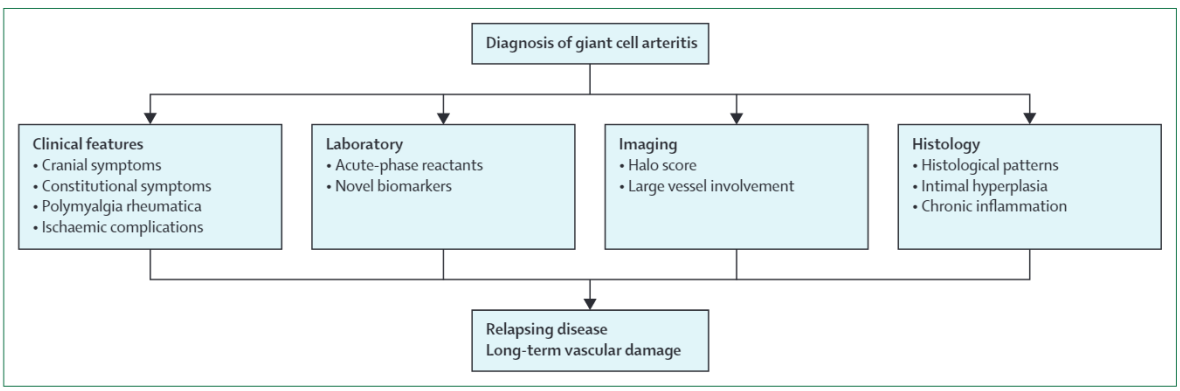

Figure: **Proposed algorithm for the stratification of patients with giant cell arteritis**

Disease stratification

The 2018 European League Against Rheumatism (EULAR) recommendations suggest to treat all newly diagnosed patients with giant cell arteritis with the same glucocorticoid regimen, with disease-modifying agents added empirically only to patients with an increased risk of steroid-related adverse effects or when a flare occurs. Apart from ischaemic complications, which might deserve intravenous steroid pulses, all patients with giant cell arteritis have the same guidance.[6] An international effort should be made to try to overcome this view of giant cell arteritis as a monolithic disease and to move towards therapy tailored to a stratified approach.

Stratification is commonly adopted in medicine, and allows for the prediction of disease outcome and the tailoring of therapy accordingly. Practically, stratification is constituted by two phases. The first phase is staging, which determines disease extent and which sites are involved. The second phase is grading, whereby disease aggressiveness and ability to cause damage are quantified. The stratification system is supported by high-quality evidence and is widely adopted in oncology, both for solid and haematological malignancies.[11] In rheumatology, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis and systemic lupus erythematosus represent, at least partly, successful examples of stratification: the involvement of critical organs, such as the kidneys, is associated with worse outcomes and dictates a more aggressive therapeutic approach than when these organs are not involved.[12,13]

With the aid of emerging evidence, we feel that a reliable system of grading and staging should also be attempted for patients with giant cell arteritis, to guide clinicians and patients with a personalised management approach. We suggest that a stratified approach to giant cell arteritis could be based on clinical, laboratory, histology, and imaging domains (figure).

Clinical and laboratory stratification

Studies on clinical predictors of disease course in patients with giant cell arteritis have reported conflicting results. It seems that patients with a strong inflammatory response, defined by highly elevated acute-phase reactants in combination with constitutional symptoms[14–16] and polymyalgia rheumatica,[17] have a higher relapse rate than patients without these characteristics, which in turn leads to high cumulative doses of glucocorticoids. Other studies indicate that constitutional and polymyalgia rheumatica features prevail in patients with extracranial large vessel involvement, who have a high tendency to relapse.[18] These data help to define a subset of patients with giant cell arteritis with large vessel involvement, who are likely to require longer treatment with glucocorticoids. Conversely, patients with predominant cranial manifestations are at increased risk for ischaemic vascular complications, which almost always occur at disease outset and require an aggressive approach with high-dose intravenous glucocorticoids;[17] nevertheless, the need for long-term glucocorticoids is probably lower in this subset than in the previously mentioned group of patients.[9,19]

In addition, novel biomarkers that outperformed traditional acute-phase reactants with regards to predicting giant cell arteritis disease course have been identified (table 1). High serum concentrations of YKL-40 (chitinase-3-like protein 1) and osteopontin at diagnosis have been linked to a relapsing disease course and high glucocorticoid requirements.[42,47] Conversely, elevated serum concentrations of VEGF, angiopoietin-1, and matrix metalloproteinase 2 (MMP-2) seem to identify patients with giant cell arteritis with a favourable disease course.[25,47] Such prognostic biomarkers, if validated, could potentially aid treatment decisions in patients with giant cell arteritis. A wide range of markers have been identified that are upregulated in patients with giant cell arteritis compared to healthy controls. These include cytokines (eg, IL-6, IL-12, IL-17, IL-23, B-cell-activating factor [BAFF]), chemokines (eg, C–C motif chemokine ligand 2 [CCL2], CCL3, CCL11, C–X–C motif chemokine ligand 9 [CXCL9]), macrophage markers (eg, soluble CD163, calprotectin, MMP-3 [also known as stromelysin-1], MMP-9), and endothelial cell markers (eg, angiopoietin-2, soluble intercellular

	Number of patients	Median (*or mean) follow-up, months	Disease outcome during follow-up			
			Relapse risk	Glucocorticoid requirement	Aortic dilatation	Mortality
Alba (2014)[15]						
Systemic inflammatory response	106	94	Increased	..	..	..
Haptoglobin	..	..	Increased	..	..	..
C-reactive protein, erythrocyte sedimentation rate, haemoglobin	..	..	No effect	..	..	..
Armstrong (2008)[20]						
Giant cells in temporal artery biopsies	92	NA	No effect	No effect	..	..
Bellan (2020)[21]						
C-reactive protein, erythrocyte sedimentation rate	19	15	No effect	..	..	..
Blockmans (2008)[22]						
C-reactive protein, erythrocyte sedimentation rate	44	47	..	..	No effect	..
de Boysson (2016)[23]						
C-reactive protein, erythrocyte sedimentation rate	139	47	..	..	No effect	..
Breuer (2013)[24]						
Temporal artery biopsy histological findings, including giant cells	65	NA	No effect	..	..	..
Burja (2019)[25]						
C-reactive protein, erythrocyte sedimentation rate, serum amyloid A	82	>12	Increased	..	..	..
MMP-2	..	..	Decreased	..	..	..
44 other biomarkers	..	..	No effect	..	..	..
Espigol-Frigole (2013)[26]						
IL-17 mRNA in temporal artery biopsies	57	54	Increased (trend)	Increased	..	..
IL-17 protein in temporal artery biopsies	..	..	Increased (trend)	Increased	..	..
Espitia (2021)[27]						
C-reactive protein	171	38	..	..	No effect	..
García-Martínez (2008)[28]						
Erythrocyte sedimentation rate	54	65	..	..	Decreased	..
Haemoglobin	..	..	..	..	Increased	..
C-reactive protein, haptoglobin, IL-6, TNF, IL-18	..	..	..	..	No effect	..
Graham (1981)[29]						
Erythrocyte sedimentation rate, haemoglobin, leukocytes	90	60*	..	..	..	No effect
Gran (2001)[30]						
C-reactive protein, erythrocyte sedimentation rate	49	64*	..	..	..	No effect
González-Gay (1997)[31]						
C-reactive protein, erythrocyte sedimentation rate	109	54	..	..	..	No effect
Hachulla (2001)[32]						
Erythrocyte sedimentation rate	133	67*	Increased (minor)	..	..	No effect

(Table 1 continues on next page)

adhesion molecule [sICAM], soluble vascular cell adhesion molecule [sVCAM], von Willebrand factor [vWF]).[25,47,49,50] Considering that these markers are upregulated during active disease, it might also be interesting to further investigate their prognostic value in giant cell arteritis.

The implications for treatment decisions are that patients with predominant cranial symptoms require

	Number of patients	Median (*or mean) follow-up, months	Disease outcome during follow-up			
			Relapse risk	Glucocorticoid requirement	Aortic dilatation	Mortality
(Continued from previous page)						
Hernández-Rodríguez (2002)[33]						
Systemic inflammatory response	75	31–40	Increased (trend)	Increased	..	..
Hernandez-Rodriguez (2004)[34]						
TNF RNA in temporal artery biopsies	29–31	18	Increased (trend)	Increased	..	..
IL-1β RNA in temporal artery biopsies	..	..	No effect	Increased	..	..
IL-6 RNA in temporal artery biopsies	..	..	No effect	No effect	..	..
Hocevar (2016)[35]						
C-reactive protein, erythrocyte sedimentation rate, leukocytes, fibrinogen, haptoglobin, serum amyloid A	68	24	Increased	..	..	..
Haemoglobin, platelets, ferritin, IL-6	..	..	No effect	..	..	..
Jud (2020)[36]						
C-reactive protein, erythrocyte sedimentation rate, fibrinogen	144	62	..	..	No effect	..
Labarca (2016)[37]						
Erythrocyte sedimentation rate, platelets, leukocytes	286	61	No effect	..	..	..
Liozon (2000)[38]						
C-reactive protein, anticardiolipin antibodies	58	34*	No effect	..	..	..
Macchioni (2019)[39]						
C-reactive protein, erythrocyte sedimentation rate	281	96	..	..	..	No effect
Haemoglobin	..	..	..	..	..	Decreased
Martinez-Lado (2011)[40]						
Erythrocyte sedimentation rate, haemoglobin, platelets, leukocytes	174	104	No effect	..	..	..
Muratore (2020)[41]						
C-reactive protein, erythrocyte sedimentation rate, platelets	87	57	No effect	No effect	..	..
Haemoglobin	..	..	No effect	Decreased	..	..
Prieto-Gonzalez (2017)[42]						
Osteopontin	76	43*	Increased	Increased	..	..
C-reactive protein	..	..	Increased	No effect	..	..
Erythrocyte sedimentation rate, haemoglobin, IL-6	..	..	No effect	No effect	..	..
Restuccia (2016)[16]						
Haemoglobin	157	62–92	Decreased	..	..	..
C-reactive protein, erythrocyte sedimentation rate, platelets	..	..	No effect	..	..	..
Giant cells, high inflammation, intraluminal thrombosis in temporal artery biopsy	..	..	Increased	..	..	..
Samson (2016)[43]						
$CD8^+$ T cells in temporal artery biopsies	42	45	..	Increased (trend)	..	..

(Table 1 continues on next page)

	Number of patients	Median (*or mean) follow-up, months	Disease outcome during follow-up			
			Relapse risk	Glucocorticoid requirement	Aortic dilatation	Mortality
(Continued from previous page)						
Samson (2018)[44]						
C-reactive protein	20	12	Increased	..	..	..
Haemoglobin	..	..	Decreased	..	..	..
Erythrocyte sedimentation rate, fibrinogen	..	..	No effect	..	..	..
Sugihara (2020)[45]						
C-reactive protein	119	12	No effect	..	..	..
Uddhammar (2002)[46]						
Erythrocyte sedimentation rate in women	136	192–244	..	..	..	Increased
Erythrocyte sedimentation rate in men	..	..	..	..	..	No effect
van Sleen (2019)[47]						
VEGF, angiopoietin-1	41	46	..	Decreased	..	..
YKL-40	..	..	..	Increased	..	..
Angiopoietin-2	..	..	..	Increased (trend)	..	..
C-reactive protein, erythrocyte sedimentation rate, IL-6, serum amyloid A, soluble Tie2 receptor, calprotectin, soluble CD163	..	..	..	No effect	..	..
van Sleen (2019)[48]						
C-reactive protein, erythrocyte sedimentation rate, IL-6, haemoglobin, platelets, leukocytes, neutrophils, monocytes, CD4, CD8, B cells, natural killer cells	42	46	..	No effect	..	..

Outcomes for specific biomarkers are presented for those with high concentrations versus those with low concentrations. Articles related to the prognostic value of biomarkers were identified by searching PubMed from inception up to Jan 21, 2021. YvS did the search and selection of the studies. First, all studies identified by the following search strategy were screened for prognostic analyses: "giant cell arteritis" AND "biomarkers" OR "markers" OR "cytokines" OR "Serum" OR "Plasma" OR "CRP" OR "ESR". Next, as many prognostic imaging studies also display standard laboratory values, all studies included in table 1 were screened for prognostic analyses using standard laboratory markers. We included only studies assessing the prognostic value of biomarkers measured at baseline, not during follow-up. IL=interleukin. MMP=matrix metalloproteinase. NA=not applicable. CD163=scavenger receptor cysteine-rich type 1 protein M130. TNF=tumour necrosis factor. VEGF=vascular endothelial growth factor.

Table 1: **List of studies evaluating potential association between specific biomarkers and disease outcome in patients with giant cell arteritis**

urgent high-dose glucocorticoids. Currently, steroid-sparing agents are considered dispensable unless a flare occurs or if there are risk factors for glucocorticoid-related adverse events.[6] Future studies should identify early additional risk factors for relapses, requirements of long-term therapy, and incipient damage such as aortic dilatation.[36] These requirements need meticulous study of disease course in the first 3–6 months, in which early divergence from remitting versus dormant or suppressed disease can be first detected. An international registry, based on the EULAR core dataset for observational research in patients with giant cell arteritis, is currently being set up to capture clinical, routine laboratory, and imaging predictors of long-term outcomes and to define different subsets of patients with giant cell arteritis.[51] This registry needs to be purposed for documenting such features of early disease severity, extent, stratification, and targeted therapy.

Histology stratification

Before the extensive introduction of vascular imaging, temporal artery biopsy has been the cornerstone for diagnosing giant cell arteritis.[52] The main limitations of this procedure are its invasiveness and the need for a surgeon to do the procedure. Its high specificity is counterbalanced by a moderate sensitivity, mainly due to the discontinuous distribution of histopathological abnormalities and sampling error.[53,54] Procedures should aim at adequate biopsy specimens of 1·5–2·0 cm length (prefixation); greater lengths are not recommended since they do not increase the diagnostic yield.[55]

Temporal artery biopsies might not only be a diagnostic aid; they might also work as a prognostic stratification tool for patients with giant cell arteritis.[56] For instance, ischaemic neuro-ophthalmic complications have been linked to the degree of intimal hyperplasia in the

inflamed temporal artery,[57,58] which, interestingly, correlates with the ultrasonographic Halo score.[59]

Histology also identifies key cellular players in the pathobiology of vascular inflammation and might allow for prognosis prediction and tailoring of therapeutic strategies to individual patients. Th1-enriched infiltrates at diagnosis might reflect a high tendency to a chronic and relapsing disease and, therefore, these patients could benefit from an early addition of a steroid-sparing agent targeting adaptive immunity.[4,60] This approach might not be needed as much in patients with Th17-enriched infiltrates, since IL-17 expression in the temporal artery is associated with low glucocorticoid requirements (table 1).[26] On the other hand, if remodelling is already present, innovative therapies targeting vascular smooth muscle cells could be used.[4,60] The comprehensive evaluation of temporal artery biopsies by novel molecular techniques, such as single-cell RNA sequencing, could potentially improve the stratification of patients with giant cell arteritis by unravelling the relevant immune pathways in great detail.

Although temporal artery biopsy is an invasive procedure, according to some, the paucity of procedural adverse events makes it suitable for monitoring purposes in selected cases. In a prospective study on 40 patients with giant cell arteritis who underwent a second temporal artery biopsy at different timepoints, it emerged that about half of those who repeated the procedure after 6 months still had histopathological findings of vasculitis, even if the disease was deemed clinically quiescent.[61] In temporal artery biopsies from these patients, lymphocytes were the most prevalent cell population. The practical implication of this observation and its reproducibility in everyday clinical practice are still debated, but it might be speculated that a more aggressive adjuvant therapeutic approach should be indicated in patients with chronically inflamed histology, regardless of clinical status.

Imaging stratification

Vascular ultrasound and magnetic resonance angiography (MRA) allow visualisation of cranial artery inflammation, whereas ultrasound, ^{18}F-fluorodeoxyglucose (^{18}F-FDG)-PET, MRA, and computer tomography angiography (CTA) are mostly used to detect large vessel giant cell arteritis.[62] A growing number of studies have evaluated the prognostic value of imaging in patients with giant cell arteritis.

A few studies found an association between large vessel involvement and increased risk of relapse and long-term glucocorticoid requirement.[45,63] In some of these studies, however, large vessel imaging was done during follow-up, probably due to a suspicion of relapsing disease, potentially leading to confounding by indication. Conversely, a single study evaluating the extent of large vessel inflammation at baseline using ^{18}F-FDG-PET total vascular score found no association with the risk of relapse.[64] An additional study showed that relapses were more common among patients with residual vascular inflammation on ^{18}F-FDG-PET at follow-up.[65]

Four studies evaluated the association between baseline large vessel involvement and risk of aortic complications. These studies suggest that aortic inflammation at baseline is an important predictor for subsequent aortic dilatation or aneurysm formation (table 2).[22,23,63,70]

Taken together, current evidence indicates that imaging findings at diagnosis might have prognostic value, particularly with aortic inflammation consistently identified as predictor for aortic complications. The association between baseline imaging findings and disease course (ie, relapse rate and glucocorticoid requirement) certainly needs to be better established with prospective and rigorous studies. Although the role of imaging in monitoring disease response to therapy is gradually emerging,[72,73] it still deserves to be better elucidated. A prospective, multicentre study evaluating the prognostic role of ultrasound at baseline in patients with giant cell arteritis (HAS-GCA) is ongoing.[74]

Application of these concepts to future clinical trials

The landmark Giant Cell Arteritis Actemra (GiACTA) trial led to the approval of tocilizumab for treating patients with giant cell arteritis by evaluating the rate of sustained glucocorticoid-free remission at 52 weeks.[10] Although GiACTA yielded positive results, it lacked adequate baseline stratification and did not evaluate long-term vascular remodelling. The same paucity of knowledge concerns methotrexate, the other disease-modifying agent included in the EULAR recommendations.[6] Questions such as whether tocilizumab or methotrexate are equally effective in patients with cranial phenotype versus patients with large vessel giant cell arteritis, or whether tocilizumab or methotrexate prevent aneurysms and other vascular damage remain unanswered.

Other molecules are currently under investigation or will be investigated shortly as steroid-sparing agents for the treatment of giant cell arteritis. This list includes drugs specifically inhibiting a single cytokine, such as the IL-17A inhibitor secukinumab, as well as the GM-CSF inhibitor mavrilimumab, and targeted synthetic agents directed against the intracellular system of the Janus kinases (JAKs).[75] Drugs belonging to this latter group have a pleiotropic effect and thereby might be effective either on dampening systemic inflammation or on the prevention of long-term vascular damage.[76] On the other hand, due to growing concerns regarding their cardiovascular side-effects,[77] adequate safety evaluations before their extensive introduction in a vulnerable, older population are mandatory.

It is essential for future interventional trials to stratify patients according to their main clinical and imaging features. Patients should be staged at baseline to assess involvement of cranial and extracranial arteries.

Quantitative scores, such as ultrasound Halo score or the PET vascular activity score (PETVAS), should be essential imaging outcomes.[65,74] With such stratification, trials could assess clinical and imaging responses of different giant cell arteritis phenotypes to the intervention and evaluate whether patients with large vessel giant cell arteritis have an outcome worse than other subsets. Such giant cell arteritis trials should not only show improved symptoms and biomarkers but also prevention of vascular damage. Long-term morphological evaluations, for example at 2–5 years, with extensive study of the aorta and its major branches by means of MRA or CTA, would be necessary.

	Baseline findings at diagnosis	Study design	Number of patients	Median (*or mean) follow-up, months	Disease outcome during follow-up		
					Relapse risk	Glucocorticoid requirement	Aortic dilatation
Bellan (2020)[21]	Aortitis (PET); ^{18}F-FDG uptake grade unclear	Retrospective	19	15	No effect	..	..
Blockmans (2008)[22]	Aorta ^{18}F-FDG uptake grade ≥2 (PET)	Retrospective†	46	47*	..	..	Increased
Czihal (2015)[18]	Involvement of subclavian or axillary arteries (ultrasound)	Retrospective	43	25*	Increased	No effect	..
de Boysson (2016)[23]	Involvement of aorta and its branches (PET)	Retrospective†	130	27 with positive baseline scan; 25 with negative baseline scan	..	..	Increased
de Boysson (2017)[66]	Involvement of aorta and its branches (PET)	Retrospective†	80	55 with large vessel giant cell arteritis; 57 without large vessel giant cell arteritis	No effect	No effect	..
de Boysson (2019)[67]	Involvement of aorta and its branches (CTA, MRA)	Retrospective	288	49 with large vessel giant cell arteritis; 43 without large vessel giant cell arteritis	Increased	Increased	..
Dumont (2020)[68]	Involvement of aorta and its branches (CTA, PET)	Retrospective	326	62	Increased	Increased	..
Espitia (2012)[69]	Aortitis (CTA)	Retrospective	22	94*	Increased	Increased	..
Muratore (2015)[63]	Involvement of subclavian arteries (CTA, MRA, PET, ultrasound)	Retrospective†	332	43 with large vessel giant cell arteritis; 55 with cranial giant cell arteritis	Increased	Increased	Increased
Muratore (2019)[70]	Aorta ^{18}F-FDG uptake grade 3 (PET)	Retrospective†	52	27	..	..	Increased
Muratore (2020)[41]	Large vessel involvement (CTA, MRA, PET, ultrasound)	Retrospective	121	57	No effect	No effect	..
Muratore (2020)[41]	Aortic arch involvement (CTA, MRA, PET)	Retrospective	121	57	Decreased		..
Sammel (2020)[64]	Extensive large vessel involvement (PET)	Prospective	21	12	Increased risk of ischaemic relapses	..	..
Samson (2018)[44]	Aortitis (CTA, PET)	Prospective	20	12	Increased	..	..
Schmidt (2008)[71]	Involvement of proximal arm arteries (ultrasound)	Retrospective	106	50	..	No effect	..
Sugihara (2020)[45]	Involvement of aorta and its branches (CTA, MRA, PET)	Retrospective	119	12	Increased	..	..

Articles related to the prognostic value of imaging were identified by searching PubMed from inception up to Jan 21, 2021. KSMvdG did the search and selection of the studies. First, all studies identified by the following search strategy were screened for prognostic analyses: "giant cell arteritis" AND "prognos*" OR "outcome" OR "response" OR "relaps*" OR "flare" OR "requir*" OR "cumulative" OR "course" OR "predict*" OR "follow*" OR "duration" OR "longterm" OR subset" AND "imaging" OR "PET" OR "FDG" OR "ultraso*" OR "sonograph*" OR "duplex" OR "CT" OR "CTA" OR "computed tomography" OR "MRA" OR "MRI" OR "magnetic resonance". 283 unique studies were identified by via the search strategy. During title and abstract screening, 32 studies were selected for full-text review and 14 studies were eventually selected for inclusion. The reference list of selected studies was also screened, which led to inclusion of one additional study. CTA=computer tomography angiography. FDG=fluorodeoxyglucose. MRA=magnetic resonance angiography. †Part of scans (possibly) done during follow-up.

Table 2: **List of studies evaluating potential association between imaging findings and disease outcome in patients with giant cell arteritis**

Search strategy and selection criteria

We did a comprehensive search of all articles published in English in PubMed, from inception up to Jan 21, 2021, regarding the role of clinical features, laboratory parameters, histology findings, and imaging in determining prognosis and long-term outcomes in patients with giant cell arteritis. All articles retrieved were read in their entirety and included if their content was relevant to the discussion. Details on the search strategy for articles included in table 1 and table 2 are reported in the respective legends.

Conclusions

When managing patients with giant cell arteritis, clinicians should not be beguiled by a short-term (3–6 months) response to high-dose glucocorticoids into ignoring longer-term disease relapses and vascular damage. Evidence suggests that giant cell arteritis is not a monolithic disease; it varies in extent and severity, so treatment should also be guided by disease stratification and by the intention to prevent poor treatment outcomes. The current one-size-fits-all strategy leads to overreliance on glucocorticoids and progression of glucocorticoid-related and disease-related complications. A new approach, however, brings challenges of disease stratification using clinical, laboratory, and imaging parameters. A giant cell arteritis registry might offer opportunities to scrutinise disease course and prognostic variables early; however, more directly purposed prospective studies incorporating the above parameters are required. Future clinical trials should be targeted at different disease strata and incorporate ultrasound, ^{18}F-FDG-PET scanning, and other imaging modalities as key outcomes.

Contributors

YvS drafted table 1 and KSMvdG drafted table 2. All authors were involved in the writing and critical review of the manuscript and approved the final version for publication.

Declaration of interests

KSMvdG reports grants from the Mandema Stipend and the FOREUM Foundation for Research in Rheumatology and personal fees from Roche, outside the submitted work. WAS reports speaker's fees and consulting fees from AbbVie, GlaxoSmithKline, Novartis, Sanofi, Roche, and Chugai. CD reports speaker's fees and consulting fees from Roche, Sanofi, AbbVie, Novartis, Lilly, Pfizer, Janssen. BD reports consulting fees from Roche, Chugai, Sanofi, and sponsorship grants for international meetings and workshops with Roche, Sanofi, AbbVie, and GlaxoSmithKline. All other authors declare no competing interests.

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