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Updates on giant cell arteritis: Pathogenesis, diagnosis and treatment

Edited by
Andreas P. Diamantopoulos and Stavros Chrysidis

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Updates on giant cell arteritis: Pathogenesis, diagnosis and treatment

Topic editors

Andreas P. Diamantopoulos — Akershus University Hospital, Norway

Stavros Chrysidis — Sydvestjysk Sygehus, Denmark

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Glucocorticoid Effects on Tissue Residing Immune Cells in Giant Cell Arteritis: Importance of GM-CSF

Annette D. Wagner[1*†], *Ulrike Wittkop*[1†], *Jessica Thalmann*[1], *Tina Willmen*[1], *Vega Gödecke*[1], *Justyna Hodam*[2], *Simon Ronicke*[1] *and Martin Zenke*[3,4]

[1] Department of Nephrology and Hypertension, Hannover Medical School, Hannover, Germany, [2] Deutsches Rotes Kreuz (DRK) Clinic for Child and Adolescent Psychiatry, Bad Neuenahr, Germany, [3] Department of Cell Biology, Institute for Biomedical Engineering, Rheinisch-Westfälische Technische Hochschule Aachen (RWTH) Aachen University Medical School, Aachen, Germany, [4] Helmholtz Institute for Biomedical Engineering, Rheinisch-Westfälische Technische Hochschule Aachen (RWTH) Aachen University, Aachen, Germany

Giant cell arteritis (GCA) is a systemic granulomatous vasculitis clinically characterized by a prompt response to glucocorticoid therapy. Dendritic cells (DCs) play a central role in the pathogenesis of the disease and are increased in temporal arteries from GCA patients. The aim of this study was to determine the effects of glucocorticoid therapy on granulomatous infiltrates and on peripheral DCs of GCA patients. Immunohistochemical staining of temporal artery specimens from 41 GCA patients revealed a rapid reduction of the number of DCs after initiation of glucocorticoid treatment. TUNEL staining was performed to quantify apoptotic S100+ DC, CD3+ T cells, and CD68+ macrophages in the granulomatous infiltrates. An increase of apoptotic cells up to 9 ± 2% after 4–5 days of glucocorticoid therapy and up to 27 ± 5% ($p < 0.001$, compared to earlier timepoints) after 6–10 days was detected. A decrease of CCL19 and CCL21 expression was observed after starting glucocorticoid therapy. Granulocyte-macrophage colony-stimulating factor (GM-CSF) expression also significantly decreased under glucocorticoid therapy. No GM-CSF expression was detected in the control specimens. Glucocorticoid therapy leads to a rapid, time-dependent reduction of DCs in temporal arteries from GCA patients and reduction of mediators for cell migration. Our data suggest GM-CSF as a novel therapeutic target of GCA.

Keywords: glucocorticoids, dendritic cells, giant cell arteritis, GM-CSF, apoptosis

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Edited by:
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Inselspital, Universitätsspital Bern, Switzerland

***Correspondence:**
Annette D. Wagner
wagner.annette@mh-hannover.de

†These authors have contributed equally to this work

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INTRODUCTION

GCA is a vasculitis predominantly affecting medium- and large-sized arteries. DCs play a significant role in the pathogenesis of large vessel vasculitides. Studies of large-vessel vasculitis have shown that activation of tissue residing DCs causes T cell and macrophage activation that subsequently leads to granuloma formation in the vessel wall (1). DCs are found at the media-adventitia junction where they act as pathogen sensors (2). Previous data showed the immediate neighborhood of DCs and activated CD4+ T cells in inflammatory lesions of temporal artery specimens from GCA patients indicating that there was a high probability of DCs being the key antigen presenting cells in GCA (3). It was shown that activated DCs stimulate autologous CD4 T cells, which produce the proinflammatory cytokine interferon-gamma (IFN-γ) and infiltrate deeply into the vascular smooth muscle cell layer, causing matrix damage (4). Granulomatous lesions in inflamed

temporal arteries harbor an array of cytokines and inflammatory mediators (1). There are two distinct immunological pathways: the interleukin (IL)-12–type 1 helper T-cell (Th1)–IFN-γ axis and the IL-6–type 17 helper T-cell (Th17)–IL-17 or IL-21 axis (5). There is evidence that Th1-related immune responses are not effectively targeted by glucocorticoid treatment (6). In fact, Th17 related cytokines have been shown to hamper both anti-inflammatory and immunosuppressant actions of glucocorticoids in peripheral lymphocytes via increased glucocorticoid-receptor beta expression (7).

Most DCs in peripheral tissues have an immature phenotype. After detection of microbial products in the presence of proinflammatory cytokines, immature DCs start to develop into mature DCs. Mature DCs develop an exceptional capacity for T cell stimulation. Immature DCs in healthy arteries fail to stimulate T cells, but DCs in polymyalgia rheumatica arteries have shown to activate T cells that originated from the GCA lesions. Therefore, it was proposed that *in situ* maturation and activation of adventitial DCs initiate and maintain T cell responses in GCA (8).

There are several factors influencing this process. Chemokines are known to be involved in the pathogenesis of GCA and are crucial for the activation of DCs. It was shown that in fully developed GCA, CCL19 expression in the vessel wall was increased 8-fold above controls and CCL21 expression was 24-fold higher than in normal arteries. In immunohistochemical studies, the major source of CCL19 and CCL21 protein was found to be CD83+ DCs (8). Also, the granulocyte macrophage colony stimulating factor (GM-CSF) is an important hematopoietic growth factor and immune modulator (9). Compared to patients with GCA in remission, patients with active GCA have increased mean levels of GM-CSF in culture supernatants of stimulated PBMCs (10).

GCA is clinically characterized by a prompt response to glucocorticoid therapy. Glucocorticoids are potent anti-inflammatory and immunosuppressive agents that act on different cells of the immune system, including T cells, monocytes, macrophages, osteoclasts and DCs (11–14). It has been shown that in sepsis glucocorticoids act on DCs by suppressing IL-12 production and therefore ameliorate inflammatory overresponse (15).

In monocytes and macrophages, glucocorticoids have the ability to down-regulate the production of a large number of cytokines, including IL-1, IL-6, IL-8, IL-12, tumor necrosis factor alpha (TNF-α), and GM-CSF (16–18). Glucocorticoids have also been reported to induce apoptosis in thymocytes and T lymphocytes (19, 20). Another study showed that glucocorticoids are potent inhibitors of bioactive IL12-p70 heterodimer production by human DCs (21). Earlier investigations indicated that glucocorticoids decrease the migratory capacity of DCs *in vitro* and reduce emigration of leukocytes from vessels (22). Further studies showed that the numbers of DCs in rat airway mucosa decrease rapidly after glucocorticoid treatment (23). It was shown that glucocorticoid treatment causes down-regulation of CD86, CD40, CD54, and MHC class II molecules on DCs (24).

To further investigate the role of DCs in the pathogenesis of GCA it was of major interest to identify the effect of glucocorticoid treatment on DCs in the granulomatous infiltrates in temporal arteries and in peripheral DCs of GCA patients.

MATERIALS AND METHODS

Patients

Temporal artery biopsy specimens for the respective immunohistochemistry, immunofluorescence techniques and in part for *in-situ* hybridization were procured from 41 GCA patients. The tissue samples used in this study were obtained prior to 2007. The tissue samples were taken from patients with a suspected GCA to establish the diagnosis. CD1c+ DC were isolated from 100 ml heparinized peripheral blood from 5 GCA patients. The peripheral blood samples were obtained in the period from 2002 to 2005. Consent by the institutional review board of the Hannover Medical School was given (No. 2752. 22.08.2001).

All the patients fulfilled the American College of Rheumatology (ACR) 1990 criteria for the classification of GCA (25). With the exception of 15 patients, bilateral temporal artery specimens were available from all. From each GCA patient 15 paraffin-embedded tissue sections were obtained: six consecutive samples were selected for TUNEL-Assay and the remaining nine consecutive samples were used for immunohistochemical studies. Temporal artery biopsies of the GCA patients showed typical relevant histopathology.

Patients included in this study were 50 years and older. These patients were treated with glucocorticoids for different time intervals before a biopsy was taken. Eight patients were untreated, 10 patients were on glucocorticoids for 1 day, 14 patients for 2 days, five patients for 3 days, three patients for 4 days, five patients for 5 days, two patients for 7 days, one patient for 10 days, and three patients were on long-term glucocorticoid therapy (longer than 14 days). These groups were selected to analyse the course of treatment since repeated biopsies in the same patient are unreasonable. The GCA patients received prednisolone orally in the following dosage once a day: 80 mg were administered in three patients, 75 mg in one patient, 70 mg in 25 patients, 60 mg in one patient and 30 mg in one patient. Only two patients received 100 mg, one patient 120 mg, five patients 300 mg, and one patient 500 mg soludecortin intravenously. Three patients with GCA were on long-term glucocorticoid therapy with a dosage of 5 mg prednisolone once a day. Samples from 11 patients without GCA served as controls. The control patients fulfilled two of the ACR criteria for GCA and were biopsied because of persisting bilateral headaches. Diagnoses of these 11 patients were: anterior ischemic optic neuropathy ($n = 2$) myocardial insufficiency ($n = 1$), polymyalgia rheumatica ($n = 3$), transitory ischemic attack ($n = 1$), stroke ($n = 2$), infectious diseases ($n = 2$). In 5/11 control patients, biopsy specimens were available from both left and right temporal arteries. Tonsillar tissue served as positive and negative control. GM-CSF detection was carried out in temporal artery biopsy specimens from 22 GCA patients that met 4–5 ACR criteria. Three of them were not treated with glucocorticoids, 10 were treated for 1 day, and nine were treated for 2 days at the time of biopsy. Eight temporal artery biopsy samples from 5 patients without GCA (with 2 ACR

criteria) served as control. Demographic data of the patients are demonstrated in **Supplementary Table 1**. Temporal artery specimens were investigated by different immunohistochemistry and immunofluorescence techniques as well as by *in-situ* hybridization. RNA was isolated from CD1c+ dendritic cells and was used for Real time PCR.

Normal tonsil tissue served as positive and negative control. It was processed and stained at the same time as the arteria samples. Unspecific reaction of the tissue with the secondary antibody was excluded by omitting the primary antibody in the negative control.

Antibodies and Staining Kits

Polyclonal Rabbit anti-cow S100 (strongly cross-reacts with human S100; DAKO Glostrup, Denmark); goat anti-mouse CCL19/MIP-3β (reacting crosswise with the human CCL19), goat anti-human CCL21/6Ckine, monoclonal mouse anti-human CD163, monoclonal anti-human GM-CSF (all from R&D Systems, Minneapolis, USA); monoclonal mouse anti-human HLA-DR (BD Biosciences, San Jose, USA); Cy2-conjugated goat anti-mouse IgG, Cy2-conjugated goat anti-rabbit IgG (both from Jackson West Grove, USA); Dako EnVision Doublestain System, AEC+ high sensitivity substrate-chromogen system, liquid DAB substrate-chromogen system (all from DAKO Carpinteria, USA); ApopTag Plus Peroxidase *in situ* Apoptosis Detection Kit, ApopTag Red Kit (both from Qbiogene, Illkirch, France).

Immunolabelling of Tissue Sections

Paraffin-embedded temporal artery specimens were deparaffinized, then microwave-heated in citrate buffer.

S100 was used several times to stain dendritic cells (26, 27). For S100 staining, endogenous peroxidase activity was blocked with hydrogen peroxidase. Tissue sections were then blocked with horse serum and stained with the rabbit anti-S-100 antibody (1:1,000) in combination with Dako EnVision Doublestain Kit and developed with AEC. For each patient and control patient, S100+ cells were counted in three different temporal artery sections at 40× magnification. Staining with anti-HLA DR, anti-CD163, anti-CCL19, anti-CCL21, and anti-GM-CSF antibodies was carried out analogously.

The number of cells per artery was counted 2-fold under the incident light microscope CK40 (Olympus Hamburg, Germany) using 40× magnification. Selected specimens were photographed by using the Soft Imaging Software (Olympus Hamburg, Germany).

The statistical evaluation of the results was realized using the program SPSS (Statistical Package for the Social Sciences). In the imaging of DC in relation to the duration of the glucocorticoid therapy all values for the number of DC per biopsy for the same duration of therapy were combined in one group, the mean value with standard deviation was determined and the groups were compared with each other.

The ApopTag Plus Peroxidase Kit was performed according to the manufacturer's instructions on 31 paraffin-embedded consecutive temporal artery specimens to quantify apoptotic cells. The number of apoptotic cells in relation to the total number of cells in the granulomatous lesions of the temporal artery cross section was counted in four different random fields at 100× magnification.

To visualize the DNA fragmentation in the nuclei, ApopTag Red Kit was applied according to the manufacturer's instructions on 12 paraffin-embedded tissue samples. To distinguish between different apoptotic cell types, sections were additionally stained either with anti-S100 Ab, anti-CD68 mAb, and anti-CD3 mAb in combination with the Cy2-conjugated secondary antibody. All 12 double-fluorescence-stained sections were evaluated by confocal microscopy. The selected tissue sections were visually cut by laser scanning along the z-axis cells in 0.5 μm slices.

For the detection of the intracellular localization of the DNA fragments the Laser Scanning-Confocal microscope MRC-600, Bio-Rad Microscience Ltd, Herts, UK was used. The system works with an argon laser and is connected to the Zeiss Axiovert 35 inverted microscope. The device has two separate detectors (photomultiplier) that can simultaneously convert the light energy of two different fluorochromes into electrical signals and display them on the computer. The special pinhole optic of a confocal microscope allows a point-like focusing in an imaging plane and makes a resolution along the optic (z) axis possible. Thus, cells can be optically sliced and intracellular structures can become visible.

The selected preparations were imaged along the z-axis at a distance of 0,5 um, resulting in 12–15 axial imaging planes per cells. The layer images were made using Comos software and recorded in two-channel imaging mode for both fluorochromes.

In the imaging of the apoptosis in relation to the duration of the glucocorticoid therapy all values for the percentage proportion of apoptotic cells for the same duration of therapy were combined in a group, the mean value with standard deviation was determined and the groups were also compared with each other. As a statistical test for assessing the differences between these defined groups the following tests were used: Bonferroni test for the number of DC and Tamhane test for the percentage of apoptotic cells. Differences were considered significant if the test yielded values of $p < 0.05$, or highly significant if it yielded values of $p < 0.01$.

In situ Hybridization

GM-CSF expression was determined by *in situ* hybridization using DakoCytomation *In Situ* Hybridization Detection System For Biotinylated Probes (DAKO Glostrup, Denmark) according to the manufacturer's protocol. GM-CSF+ cells were counted in two different temporal artery sections at 40× magnification.

Isolation of Peripheral CD 1c+ Dendritic Cells, RNA Isolation, and Real-Time PCR for CSF2RB

100 ml of heparinized blood was used to isolate peripheral blood mononuclear cells (PBMC) using Ficoll-Hypaque density gradient centrifugation. Positive selection of CD1c+ peripheral DC was performed by using the CD1c (BDCA-1) Dendritic Cell Isolation Kit (Miltenyi, Bergisch-Gladbach, Germany) according to the manufacturer's protocol. To obtain total RNA, the NucleoSpin RNA II Kit (Macherey-Nagel, Düren, Germany)

was applied according to manufacturer's instructions. Residues of genomic DNA in RNA samples were digested with RQ1 (Promega, Madison, USA). For Real-time PCR, 0.6 μg total RNA was subjected to reverse transcription using the Reverse Transcription Core Kit with random hexamers (Eurogentec, Seraing, Belgium) according to manufacturer's instructions. Subsequent real-time PCR was performed in an ABI Prism 7000 (Applied Biosystems, Darmstadt, Germany) with gene-specific primers for the colony stimulating factor 2 receptor beta common subunit (CSF2RB) also of the GM-CSF receptor and the housekeeping gene RPS9 in combination with SYBRGreen chemistry (Eurogentec, Seraing, Belgium). Order and sequence information of the oligonucleotides used for real-time PCR is supplied in **Supplementary Table 2**. Data were analyzed using Q-gene software.

RESULTS

Reduction of DC Under Glucocorticoid Therapy

The majority of DCs identified by immunohistochemical studies using anti-S100 Ab were located in granulomatous infiltrates (MHC II staining), in the adventitial layer and in a circular array along the internal and external elastic lamina (**Figure 1A**). In different temporal artery specimens DCs appeared in clusters. An inverse relation was observed between the length of glucocorticoid therapy and DC number (**Figure 1B**). Temporal arteries from both sides of an untreated GCA patient were examined. 135 DCs were present in a cross section of the right temporal artery, and 128 DCs in the cross section of the left side. After 1 day of glucocorticoid therapy 46 ± 21 DCs (mean ± standard deviation, $n = 16$ temporal arteries) were present in one tissue cross section. After 2–4 days only 20 ± 16 DCs ($n = 30$, $p < 0.001$) were detectable. Further decrease was monitored at later timepoints. Under long-term glucocorticoid therapy (>10 days) 9 ± 3 DCs ($n = 5$ temporal arteries) were determined ($p = 0.004$) in comparison to patients after 1 day of glucocorticoid treatment. An increase of monocyte-macrophage scavenger receptor CD163 was observed under glucocorticoid therapy that inversely correlates with the number of S100+ cells and the duration of glucocorticoid exposure (**Figure 1A**).

Glucocorticoid Therapy Induces Apoptosis

An increase of apoptotic cells determined by TUNEL assay was seen with prolonged glucocorticoid therapy (**Figure 2A**). Glucocorticoid therapy induces apoptosis predominantly in inflammatory cell infiltrates. The percentage of apoptotic cells rose after 4–5 days of glucocorticoid to 9 ± 2%. From day 6 to day 10 glucocorticoids led to a significant increase in the amount of apoptotic cells, 27 ± 5% ($p < 0.001$, compared to the earlier timepoints) (**Figure 2B**). Double immunofluorescence demonstrated that CD3+ T cells and CD68+ macrophages (**Figure 2C**) underwent apoptosis. Confocal microscopy confirmed that DNA-fragments are intracellularly located in apoptotic S100+ DC. One example of intracellular DNA-fragmentation in DC is depicted in **Figure 2D** and in **Supplementary Material Presentation**.

Reduction of CCL19 and CCL21 Expression in the Temporal Artery Specimens

CCL19 and CCL21 serve as ligands for CCR7, which is prominently expressed on mature DC and the CCL19/21 – CCR7 system balances immunity and tolerance (28). To investigate the surface expression of both molecules on cells of the granulomatous infiltrates, immunohistochemistry was performed on temporal artery specimens of glucocorticoid-untreated and treated GCA patients and patients negative for GCA (controls). Compared to untreated control patients, high levels of CCL19+ cells in granulomatous infiltrates were observed in untreated GCA patients. After the onset of glucocorticoid therapy, the percentage of CCL19+ cells started to decrease. Continuous reduction was observed with increased duration of therapy (**Figure 3A**). The same tendency was observed for the percentage of CCL21+ cells (**Figure 3B**).

Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) Expression Decreases Under Glucocorticoid Therapy

Expression of GM-CSF in temporal artery biopsy specimens from GCA patients that where either not treated (0 days), or 1 day or 2 days treated, was analyzed by *in situ* hybridization on mRNA level and by immunohistochemistry on protein level. Both techniques delivered concurrent results for the expression of GM-CSF+ cells. In untreated patients about 172 GM-CSF+ cells were detected (mRNA: 169 ± 7.4, protein: 176 ± 7.9; $n = 3$) in the arterial cell wall. Already after 1 day of glucocorticoid treatment a reduction of GM-CSF+ cells was observed (mRNA: 104 ± 2.9, protein: 112 ± 4.0; $n = 10$). After 2 days of treatment <50% GM-CSF+ cells (mRNA: 76 ± 1.6, protein: 80 ± 1.9; $n = 9$) were detected, as compared to untreated patients (**Figure 4**). A significantly reduced CSF2RB expression was observed in peripheral blood CD1c+ DCs (**Table 1**).

DISCUSSION

Administration of glucocorticoids suppresses the accumulation of DCs and leads to a rapid, time-dependent normalization of DCs in temporal arteries from GCA patients. The findings reported here suggest that this effect is mediated by induction of apoptosis since the percentage of apoptotic cells increased continuously according to the length of glucocorticoid application. TUNEL positive cells were mainly located in the inflammatory lesions. Apoptosis could be the central mechanism reducing DC and other inflammatory cells in temporal arteries in GCA. Interestingly, mature DCs express a pro-apoptotic glucocorticoid receptor isoform, which is not present in immature DCs (29). Therefore, we conclude that glucocorticoids effectively suppress inflammation in GCA by diminishing cell-mediated immunity. Exposure of macrophages to glucocorticoids for 24 h specifically enhances the uptake of apoptotic leukocytes by both human and murine macrophage population (30). CD163 is used as *in vivo* marker for alternatively activated macrophage (31). Its expression is suppressed by pro-inflammatory mediators such as LPS,

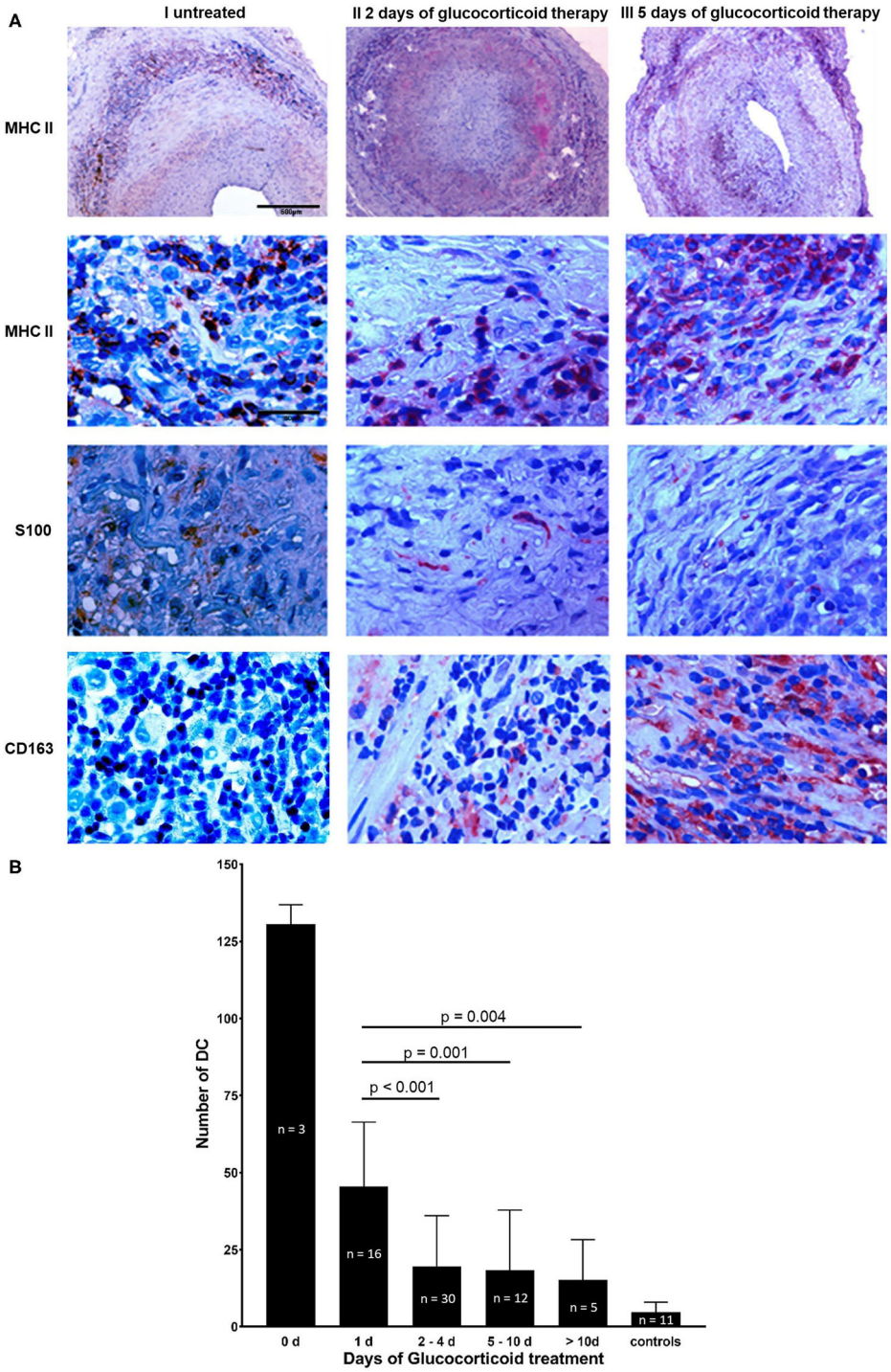

FIGURE 1 | Reduction of DC under glucocorticoid therapy. **(A)** Temporal artery biopsy sections from three individual patients with GCA. Cross sections from a newly diagnosed untreated GCA patient are shown in column I, sections of a GCA patient after 2 days of glucocorticoid therapy are depicted in column II and tissue sections of a GCA patient 5 days after the initiation of glucocorticoid treatment are demonstrated in column III. Cross sections were stained with anti-MHC II mAb (row 1, 2), anti-S100 Ab (row 3), and anti-CD163 mAb (row 4). Cells positive for the particular epitope are indicated by red stain. Nuclei were stained with haematoxylin and eosin. Scale bar = 500 μm in row 1, scale bar = 50 μm in row 2–4. **(B)** Number of S100+ DC in 75 paraffin-embedded consecutive temporal artery sections from 41 GCA patients and 11 control patients. For each patient and control patient, S100+ cells were counted in three different temporal artery sections at 40× magnification. Patients were grouped depending on the duration of treatment (0, 1, 2–4, 5–10, >10, controls).

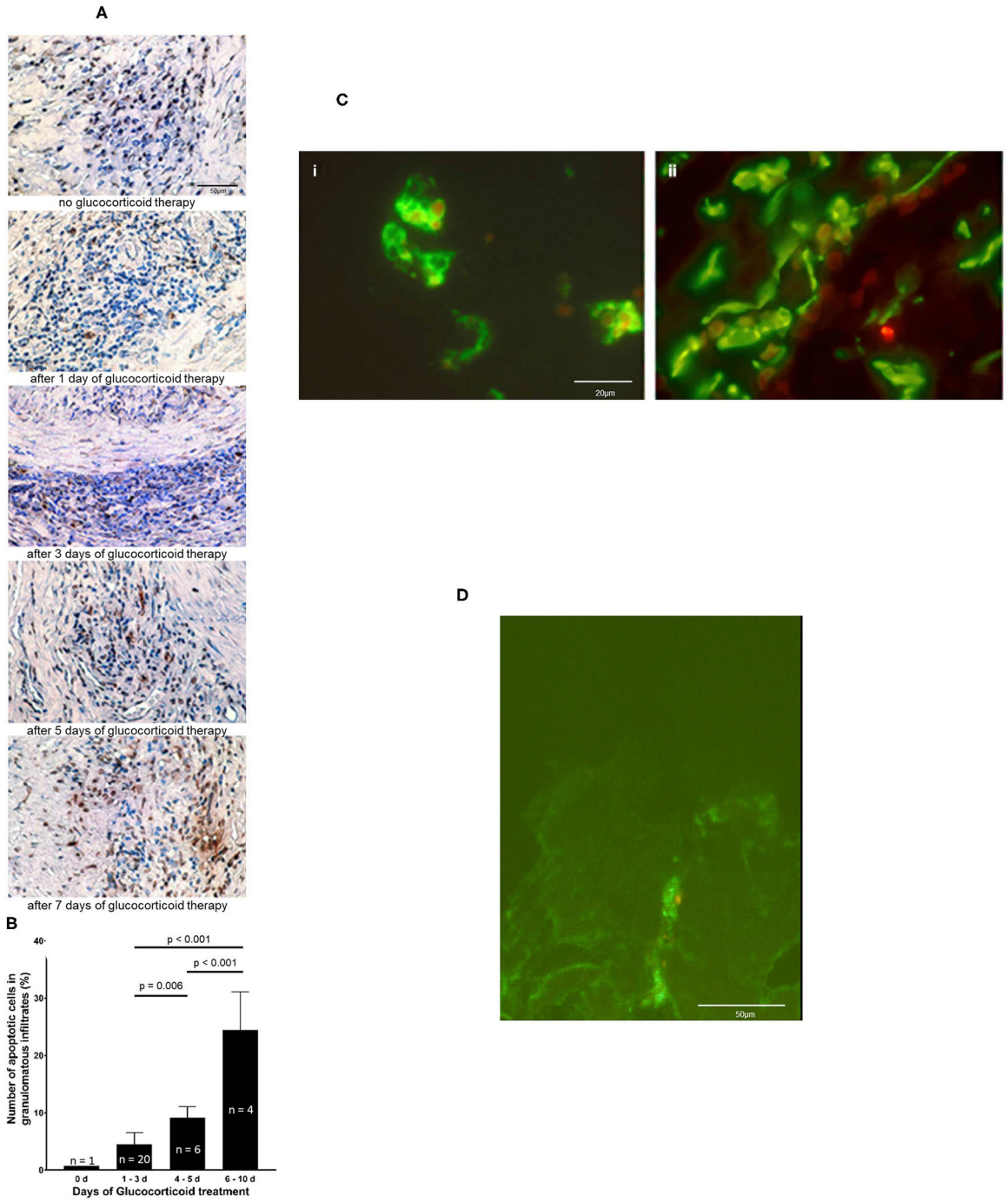

FIGURE 2 | Glucocorticoid therapy induces apoptosis. **(A)** DNA fragmentation of apoptotic cells (brown stain) is demonstrated by applying TUNEL assay on temporal artery sections of five GCA patients. Nuclei were stained with haematoxylin and eosin. Scale bar = 50 µm. **(B)** The number of TUNEL-positive cells was quantified in 31 paraffin-embedded consecutive temporal artery specimens. For each patient and control patient, TUNEL-positive cells and nuclei of all cells in four random fields (magnification 100×) of each specimen were counted. The percentages of TUNEL-positive cells of all cells in the samples were calculated. **(C)** Demonstration of intracellular DNA fragmentation in CD3+ cells (i) and CD68+ cells (ii) in a temporal artery biopsy specimen from a patient with GCA 5 days after glucocorticoid treatment. T cells and macrophages are stained with anti-CD3 mAb and anti-CD68 mAb (green fluorescene), respectively. Applying the ApopTag Red Kit, rhodamine-labeled DNA fragmentation (red fluorescene) was identified. Scale bar = 20 µm. **(D)** Demonstration of intracellular DNA fragmentation in tissue-residing DC in a temporal artery biopsy specimen from a patient with GCA 5 days after glucocorticoid treatment. Confocal microscopy reveals rhodamine-labeled DNA fragmentation (red fluorescence) within DC, that is stained with anti-S100 Ab (green fluorescence). Scale bar = 50 µm.

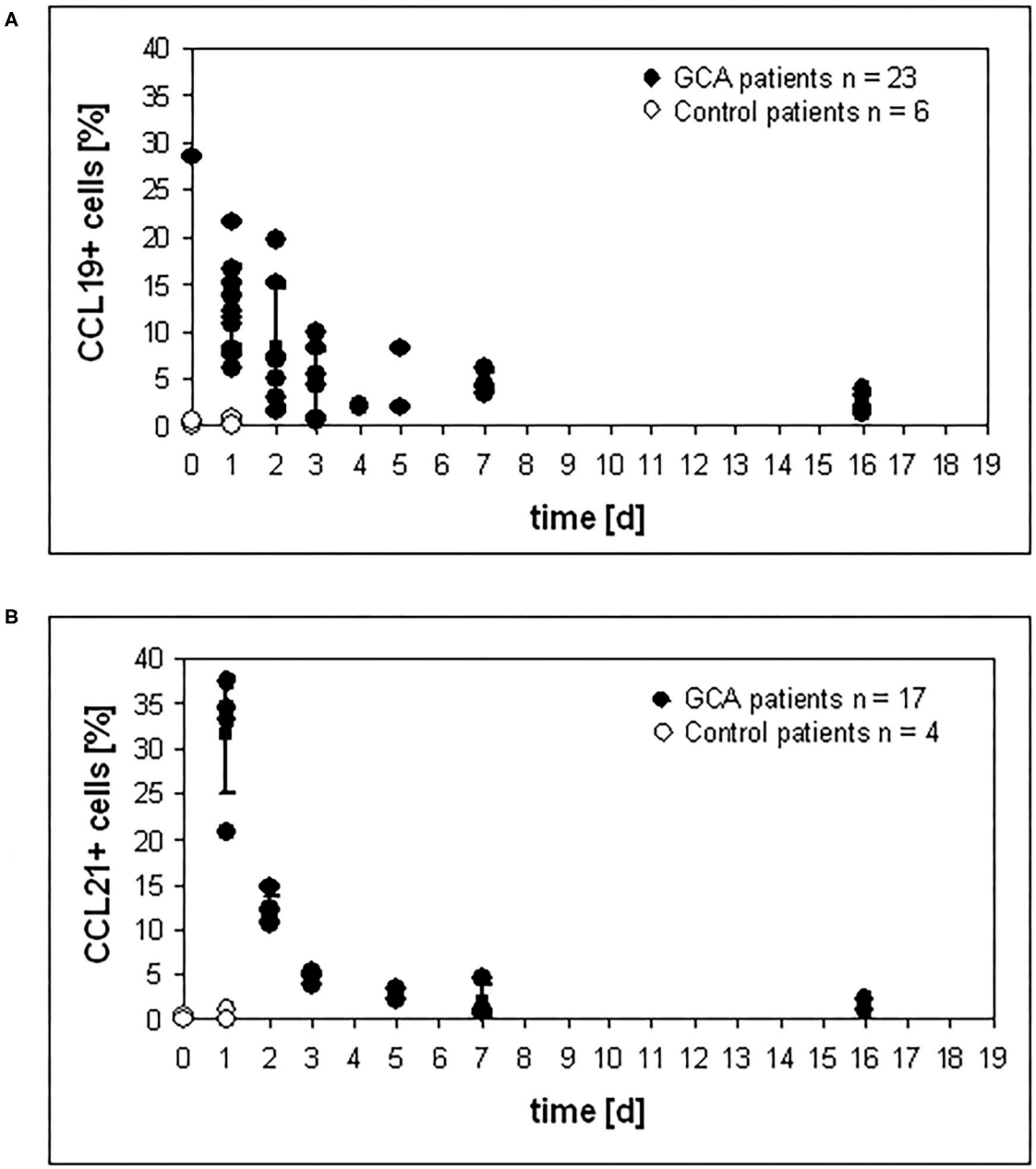

FIGURE 3 | Reduction of CCL19 and CCL21 expression under glucocorticoid therapy. Temporal artery sections of patients were stained with **(A)** anti-CCL19 mAb and **(B)** anti-CCL21 mAB, respectively, and numbers of positive cells were determined in three sections. For each patient and control patient, positive cells were counted in three different temporal artery sections.

IFN-γ and TNF-α, whereas IL-6 and the anti-inflammatory cytokine IL-10 strongly up-regulate CD163 expression (32). Moreover, CD163 mediates IL-10 release itself (33). The observed increase of CD163 in temporal artery biopsy specimens from glucocorticoid treated GCA patients further supports our conclusion.

In many cell types, glucocorticoid receptor activation leads to G_1 cell cycle arrest, this cytostatic condition is often reversible, such that upon withdrawal of glucocorticoid the cells re-enter the cell cycle (34). In other cell types, glucocorticoid treatment is cytotoxic and irreversible and results in programmed cell death or apoptosis (35). The transcriptional regulatory mechanisms underlying the cytostatic vs. the cytotoxic effects of the glucocorticoid receptor and the target genes affected by the receptor need to be determined. In summary, the described glucocorticoid-induced apoptosis of DC, macrophages and T

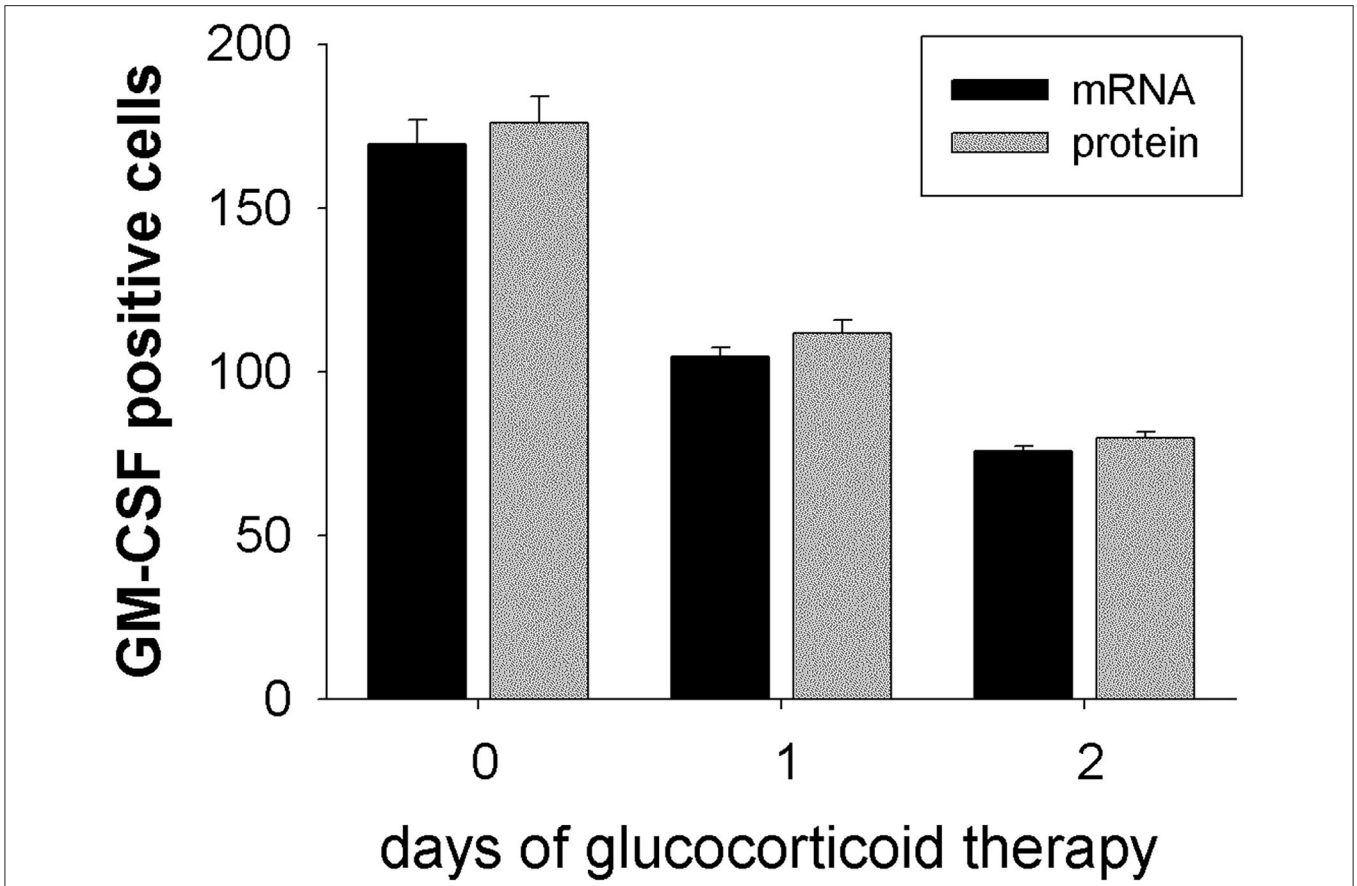

FIGURE 4 | GM-CSF expression is down-regulated under glucocorticoid therapy. GM-CSF expression was determined on mRNA level by *in situ* hybridization (black bars) and on protein level by immunohistochemistry using anti-GM-CSF mAb (gray bars). Temporal artery biopsy specimens were obtained from GCA patients without glucocorticoid treatment (0 days; $n = 3$), or after 1 day of therapy ($n = 10$), or after 2 days of therapy ($n = 9$). For each patient GM-CSF+ cells were counted in two different temporal artery sections at 40× magnification.

cells in the granulomatous lesions seem to be an important mechanism for the immunosuppressive effect and especially the control of autoreactivity and autoimmunity.

In contrast, disease relevant tissue residing IL-12-IFN-γ-producing Th1 cells are most likely being protected from apoptosis. Plasma levels of IFN-γ are elevated in untreated GCA cases and remain elevated after corticosteroid therapy (1). Accordingly, these cells can cause disease relapse after discontinuation of GC treatment (6). This might be explained by the fact that in some cell types glucocorticoid receptor activation leads to G1 cell cycle arrest. This cytostatic condition is reversible, such that upon withdrawal of glucocorticoid therapy the cell re-enters the cell cycle (34). In other cell types, glucocorticoid treatment is cytotoxic and irreversible resulting in programmed cell death or apoptosis (35).

Another important mechanism detected in our study is the inhibition of leukocyte migration. CCL19 and CCL21 lead to migration of mature DC into lymphatic tissues for antigen presentation (26). It was hypothesized that granulomatous infiltrates in temporal arteries of GCA patients serve as a "pathologic" lymphatic tissue (36). Reduced expression of CCL19 and CCL21 under glucocorticoid therapy could thus explain reduced numbers of DCs in the granulomatous lesions by inhibition of migration and activation of DCs. Glucocorticoids also suppress the trafficking of immune cells *in vivo* by increasing the protein expression of macrophage migratory inhibitory factor (37).

TABLE 1 | Glucocorticoid therapy reduces CSF2RB expression in peripheral blood CD1c+ DCs.

	Mean Normalized Expression (×10.000)	
	Day 0	**Day 2**
CSF2RB	1914.12	0.50

Under inflammatory conditions, activated CD4+ T-helper cells produce large amounts of GM-CSF at systemic level. In this way an emergency myelopoiesis drives macrophages and dendritic cells or common monocyte precursors into cell cycle and releases increased amounts of classical monocytes into the blood. In peripheral blood these monocytes again

differentiate into monocyte-derived dendritic cells. It is known that GM-CSF controls some common and peripheral dendritic cell functions (38).

In tissue samples from GCA patients GM-CSF was predominantly expressed in the adventitial layer, where we also detected the granulomatous infiltrates. Under glucocorticoid therapy we found a significant reduction of GM-CSF+ cells in the arterial wall. As this factor induces proliferation and activation of various types of leukocytes, the downregulation of GM-CSF might also contribute to the observed decrease of DC numbers in GCA under glucocorticoid treatment. Secondly, GM-CSF is a locally expressed mediator that has the capacity of recruiting circulating leukocytes. Real-time PCR of peripheral CD1c+ DCs in GCA patients revealed a down-regulation of CSF2RB. CSF2RB is known as the common beta-subunit of GM-CSF, IL-3 and IL-5-receptors (39). Glucocorticoid therapy may therefore prevent the injured artery in GCA from recruiting further DCs. This conclusion is also in line with decreasing numbers of DCs in the examined biopsy specimens. Furthermore, GM-CSF has additional angiogenic properties (40). Blockade of GM-CSF by GC therapy might inhibit angiogenesis of the vasa vasorum in GCA and thereby reduce leukocyte trafficking.

Granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) have proinflammatory activities. In mouse models of rheumatoid arthritis it was shown that antagonism of G-CSF or GM-CSF significantly reduced disease activity (41). In addition, it was shown that G-CSF and GM-CSF administration can exacerbate rheumatoid arthritis, and their antagonism has a potential to reduce disease activity in RA (42). Therefore, we hypothesize, that antagonism of G-CSF or GM-CSF might also be an effective way of treating other inflammatory disorders, such as GCA. We strongly hope that our data support the initiation of a clinical trial regarding GM-CSF antagonization in GCA.

In summary, the described glucocorticoid-induced apoptosis of DC, macrophages and T cells in the granulomatous lesions seem to be an important mechanism for the immunosuppressive effect in GCA. In future studies it will have to be evaluated whether other mechanisms contribute to this effect. Further understanding of these mechanisms may allow tailoring therapies that facilitate the resolution of the inflammatory process in GCA.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethikkommission der Medizinischen Hochschule Hannover. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

ADW and UW substantially contributed equally to conceptualization, formal analysis, resources, supervision, and writing of the original draft. JT and JH substantially contributed to formal analysis, investigation, and reviewing and editing of the manuscript. TW contributed to the preparation of the tables and editing of the manuscript. VG and SR substantially contributed to project administration and reviewing and editing of the manuscript. MZ substantially contributed to conceptualization, project administration, supervision, and reviewing and editing of the manuscript. All the authors revised the paper and approved the final version of the article to be published.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.709404/full#supplementary-material

REFERENCES

1. Weyand CM, Goronzy JJ. Immune mechanisms in medium and large-vessel vasculitis. *Nat Rev Rheumatol.* (2013) 9:731–40. doi: 10.1038/nrrheum.2013.161
2. Pryshchep O, Ma-Krupa W, Younge BR, Goronzy JJ, Weyand CM. Vessel-specific toll-like receptor profiles in human medium and large arteries. *Circulation.* (2008) 118:1276–84. doi: 10.1161/CIRCULATIONAHA.108.789172
3. Wagner AD, Wittkop U, Prahst A, Schmidt WA, Gromnica-Ihle E, Vorpahl K, et al. Dendritic cells co-localize with activated CD4+ T cells in giant cell arteritis. *Clin Exp Rheumatol.* (2003) 21:185–92.
4. Han JW, Shimada K, Ma-Krupa W, Johnson TL, Nerem RM, Goronzy JJ, et al. Vessel wall-embedded dendritic cells induce T-cell autoreactivity and initiate vascular inflammation. *Circ Res.* (2008) 102:546–53. doi: 10.1161/CIRCRESAHA.107.161653
5. Weyand CM, Younge BR, Goronzy JJ. IFN-γ and IL-17: the two faces of T-cell pathology in giant cell arteritis. *Curr Opin Rheumatol.* (2011) 23:43–9. doi: 10.1097/BOR.0b013e32833ee946
6. Deng J, Younge BR, Olshen RA, Goronzy JJ, Weyand CM. Th17 and th1 T-cell responses in giant cell arteritis. *Circulation.* (2010) 121:906–15. doi: 10.1161/CIRCULATIONAHA.109.872903
7. Vazquez-Tello A, Halwani R, Hamid Q, Al-Muhsen S. Glucocorticoid receptor-beta up-regulation and steroid resistance induction by IL-17 and IL-23 cytokine stimulation in peripheral mononuclear cells. *J Clin Immunol.* (2013) 33:466–78. doi: 10.1007/s10875-012-9828-3
8. Ma-Krupa W, Jeon MS, Spoerl S, Tedder TF, Goronzy JJ, Weyand CM. Activation of arterial wall dendritic cells and breakdown of self-tolerance in giant cell arteritis. *J Exp Med.* (2004) 199:173–83. doi: 10.1084/jem.20030850
9. Shi Y, Liu CH, Roberts AI, Das J, Xu G, Ren G, et al. Granulocyte-macrophage colony-stimulating factor (GM-CSF) and T-cell responses: what we do and don't know. *Cell Res.* (2006) 16:126–33. doi: 10.1038/sj.cr.7310017

10. Terrier B, Geri G, Chaara W, Allenbach Y, Rosenzwajg M, Costedoat-Chalumeau N, et al. Interleukin-21 modulates Th1 and Th17 responses in giant cell arteritis. *Arthritis Rheum.* (2012) 64:2001–11. doi: 10.1002/art.34327
11. Zacharchuk CM, Merćep M, Chakraborti PK, Simons SS, Ashwell JD. Programmed T lymphocyte death. Cell activation- and steroid-induced pathways are mutually antagonistic. *J Immunol.* (1990) 145:4037–45.
12. Blotta MH, DeKruyff RH, Umetsu DT. Corticosteroids inhibit IL-12 production in human monocytes and enhance their capacity to induce IL-4 synthesis in CD4+ lymphocytes. *J Immunol.* (1997) 158:5589–95.
13. Weinstein RS, Jilka RL, Michael Parfitt A, Manolagas SC. Inhibition of osteoblastogenesis and promotion of apoptosis of osteoblasts end osteocytes by glucocorticoids potential mechanisms of their deleterious effects on bone. *J Clin Invest.* (1998) 102:274–82. doi: 10.1172/JCI2799
14. Piemonti L, Monti P, Allavena P, Sironi M, Soldini L, Leone BE, et al. Glucocorticoids affect human dendritic cell differentiation and maturation. *J Immunol.* (1999) 162:6473–81.
15. Li CC, Munitic I, Mittelstadt PR, Castro E, Ashwell JD. Suppression of dendritic cell-derived IL-12 by endogenous glucocorticoids is protective in LPS-induced sepsis. *PLoS Biol.* (2015) 13:e1002269. doi: 10.1371/journal.pbio.1002269
16. Joyce DA, Kloda A, Steer JH. Dexamethasone suppresses release of soluble TNF receptors by human monocytes concurrently with TNF-α suppression. *Immunol Cell Biol.* (1997) 75:345–50. doi: 10.1038/icb.1997.53
17. Kunicka JE, Talle MA, Denhardt GH, Brown M, Prince LA, Goldstein G. Immunosuppression by glucocorticoids: inhibition of production of multiple lymphokines by *in vivo* administration of dexamethasone. *Cell Immunol.* (1993) 149:39–49. doi: 10.1006/cimm.1993.1134
18. Almawi WY, Beyhum HN, Rahme AA, Rieder MJ. Regulation of cytokine and cytokine receptor expression by glucocorticoids. *J Leukoc Biol.* (1996) 60:563–72. doi: 10.1002/jlb.60.5.563
19. Gruber J, Sgonc R, Hu YH, Beug H, Wick G. Thymocyte apoptosis induced by elevated endogenous corticosterone levels. *Eur J Immunol.* (1994) 24:1115–21. doi: 10.1002/eji.1830240516
20. Brunetti M, Martelli N, Colasante A, Piantelii M, Musiani P, Aiello FB. Spontaneous and glucocorticoid-induced apoptosis in human mature T lymphocytes. *Blood.* (1995) 86:4199–205. doi: 10.1182/blood.V86.11.4199.bloodjournal86114199
21. Vieira PL, Kaliński P, Wierenga EA, Kapsenberg ML, de Jong EC. Glucocorticoids inhibit bioactive IL-12p70 production by *in vitro*-generated human dendritic cells without affecting their T cell stimulatory potential. *J Immunol.* (1998) 161:5245–51.
22. Perretti M, Ahluwalia A. The microcirculation and inflammation: site of action for glucocorticoids. *Microcirculation.* (2000) 7:147–61. doi: 10.1111/j.1549-8719.2000.tb00117.x
23. Brokaw JJ, White GW, Baluk P, Anderson GP, Umemoto EY, Mcdonald DM, et al. Glucocorticoid-induced apoptosis of dendritic cells in the rat tracheal mucosa. *Am J Respir Cell Mol Biol.* (1998) 19:598–605. doi: 10.1165/ajrcmb.19.4.2870
24. Pan J, Ju D, Wang Q, Zhang M, Xia D, Zhang L, et al. Dexamethasone inhibits the antigen presentation of dendritic cells in MHC class II pathway. *Immunol Lett.* (2001) 76:153–61. doi: 10.1016/S0165-2478(01)00183-3
25. Hunder GG, Bloch DA, Michel BA, Stevens MB, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. *Arthritis Rheum.* (1990) 33:1122–8. doi: 10.1002/art.1780330810
26. Zeid NA, Muller HK. S100 positive dendritic cells in human lung tumors associated with cell differentiation and enhanced survival. *Pathology.* (1993) 25:338–43. doi: 10.3109/00313029309090853
27. Demetris AJ Sever C, Kakizoe S, Oguma S, Starzl TE, Jaffe R. S100 positive dendritic cells in primary biliary cirrhosis and other chronic inflammatory liver diseases. Relevance to pathogenesis? *Am J Path.* (1989) 134:741–7.
28. Förster R, Davalos-Misslitz AC, Rot A. CCR7 and its ligands: balancing immunity and tolerance. *Nat Rev Immunol.* (2008) 8:362–71. doi: 10.1038/nri2297
29. Cao Y, Bender IK, Konstantinidis AK, Shin SC, Jewell CM, Cidlowski JA, et al. Glucocorticoid receptor translational isoforms underlie maturational stage-specific glucocorticoid sensitivities of dendritic cells in mice and humans. *Blood.* (2013) 121:1553–62. doi: 10.1182/blood-2012-05-432336
30. Liu Y, Cousin JM, Hughes J, Van Damme J, Seckl JR, Haslett C, et al. Glucocorticoids promote nonphlogistic phagocytosis of apoptotic leukocytes. *J Immunol.* (1999) 162:3639–46.
31. Goerdt S, Orfanos CE. Other functions, other genes: alternative activation of antigen-presenting cells. *Immunity.* (1999) 10:137–42. doi: 10.1016/S1074-7613(00)80014-X
32. Buechler C, Ritter M, Orsó E, Langmann T, Klucken J, Schmitz G. Regulation of scavenger receptor CD163 expression in human monocytes and macrophages by pro- and antiinflammatory stimuli. *J Leukoc Biol.* (2000) 67:97–103. doi: 10.1002/jlb.67.1.97
33. Philippidis P, Mason JC, Evans BJ, Nadra I, Taylor KM, Haskard DO, et al. hemoglobin scavenger receptor CD163 mediates interleukin-10 release and heme oxygenase-1 synthesis: antiinflammatory monocyte-macrophage responses *in vitro*, in resolving skin blisters *in vivo*, and after cardiopulmonary bypass surgery. *Circ Res.* (2004) 94:119–26. doi: 10.1161/01.RES.0000109414.78907.F9
34. Jiang W, Zhu Z, Bhatia N, Agarwal R, Thompson HJ. Mechanisms of energy restriction: effects of corticosterone on cell growth, cell cycle machinery, and apoptosis. *Cancer Res.* (2002) 62:5280–7.
35. Rogatsky I, Hittelman AB, Pearce D, Garabedian MJ. Distinct glucocorticoid receptor transcriptional regulatory surfaces mediate the cytotoxic and cytostatic effects of glucocorticoids. *Mol Cell Biol.* (1999) 19:5036–49. doi: 10.1128/MCB.19.7.5036
36. Ma-Krupa W, Dewan M, Jeon MS, Kurtin PJ, Younge BR, Goronzy JJ, et al. Trapping of misdirected dendritic cells in the granulomatous lesions of giant cell arteritis. *Am J Pathol.* (2002) 161:1815–23. doi: 10.1016/S0002-9440(10)64458-6
37. Fingerle-Rowson G, Koch P, Bikoff R, Lin X, Metz CN, Dhabhar FS, et al. Regulation of macrophage migration inhibitory factor expression by glucocorticoids *in vivo*. *Am J Pathol.* (2003) 162:47–56. doi: 10.1016/S0002-9440(10)63797-2
38. Lutz MB, Strobl H, Schuler G Romani N. GM-CSF monocyte-derived cells and langerhans cells part of the dendritic cell family. *Front Immonol.* (2017) 8:1388. doi: 10.3389/fimmu.2017.01388
39. Sakamaki K, Miyajima I, Kitamura T, Miyajima A. Critical cytoplasmic domains of the common beta subunit of the human GM-CSF, IL-3 and IL-5 receptors for growth signal transduction and tyrosine phosphorylation. *EMBO J.* (1992) 11:3541–9. doi: 10.1002/j.1460-2075.1992.tb05437.x
40. Bikfalvi A, Han ZC. Angiogenic factors are hematopoietic growth factors and vice versa. *Leukemia.* (1994) 8:523–9.
41. Cook AD, Louis C, Robinson MJ, Saleh R, Sleeman MA, Hamilton JA. Granulocyte macrophage colony-stimulating factor receptor alpha expression and its targeting in antigen-induced arthritis and inflammation. *Arthritis Res Ther.* (2016) 18:287. doi: 10.1186/s13075-016-1185-9
42. Di Franco M, Gerardi MC, Lucchino B, Conti F. Mavrilimumab: an evidence based review of ist potential in the treatment of rheumatoid arthritis. *Core Evid.* (2014) 9:41–8. doi: 10.2147/CE.S39770

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Impact of Giant Cell Arteritis and Its Treatment on the Patient's Quality of Life: A Single-Center Self-Assessment Study

Hubert de Boysson [1,2], Clivia Barakat [1], Anael Dumont [1,2], Jonathan Boutemy [1], Nicolas Martin Silva [1], Gwénola Maigné [1], Alexandre Nguyen [1,2], Amandine Lavergne [1], Paul Castan [1], Sophie Gallou [1], Audrey Sultan [1], Samuel Deshayes [1,2] and Achille Aouba [1,2]*

[1] Department of Internal Medicine, Caen University Hospital, Caen, France, [2] Caen University-Normandie, Caen, France

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Christian Dejaco,
Medical University of Graz, Austria

Reviewed by:
Angelika Lackner,
Medical University of Graz, Austria
Luca Quartuccio,
University of Udine, Italy

***Correspondence:**
Hubert de Boysson
deboysson-h@chu-caen.fr

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Little is known about the impact of giant cell arteritis (GCA) and its treatment on patient-reported physical, mental, and psychic quality of life (QoL). In this monocentric study, a questionnaire was sent to the 100 last patients diagnosed with GCA and followed-up in a single tertiary center. Their physical, mental and psychic status were self-assessed via close-ended questions, the 12-item short form survey (SF-12) and the 15-item geriatric depression scale (GDS). We aimed to identify parameters that were significantly associated with moderate-to-severe disability in both physical and mental domains. Ninety patients were analyzable. Moderate to severe physical disability was found in 41 (46%) patients. In multivariate analysis, walking difficulties (OR, 95% CI 8.42 [2.98–26.82], $p < 0.0001$), muscle mass and strength reduction (OR, 95% CI 4.38 [1.37–16.31], $p = 0.01$) and age >80 (OR, 95% CI 4.21 [1.44–13.61], $p = 0.008$) were independent findings associated with moderate to severe physical disability. Moderate to severe mental disability was found in 30 (33%) patients. In multivariate analysis, depressive mood (OR, 95% CI 11.05 [3.78–37.11], $p < 0.0001$), felt adverse events attributable to glucocorticoids (OR, 95% CI 10.54 [1.65–213.1], $p = 0.01$) and use of immune-suppressants (OR, 95% CI 3.50 [1.14–11.87], $p = 0.03$) were independent findings associated with moderate to severe mental disability. There was a statistically significant negative correlation between GDS and the physical and/or mental disability scores (GDS and PCS-12: $r = -0.33$, $p = 0.0013$; GDS and MCS-12: $r = -0.36$, $p = 0.0005$). In conclusion, this study identified via a self-assessment of patients with GCA some medical and modifiable findings that significantly affect their physical and mental quality of life. A better knowledge of these factors may help improve the care of GCA patients.

Keywords: giant-cell arteritis, patient report outcome, auto-questionnaire, quality of life, physical disabilities, mental disabilities

INTRODUCTION

Giant cell arteritis (GCA) is the most frequent systemic vasculitis, typically affecting patients over 50. The mean age of GCA diagnosis in different studies ranges between 70 and 80 years old (1). The disease burden includes a chronic course and a subsequent prolonged treatment (2, 3), especially because of a high risk of relapse that affects approximately half of patients (4). Glucocorticoids (GCs) remain the cornerstone of treatment, and recent studies have indicated that their management has not significantly changed over the last six decades (3, 5, 6). The GC duration still ranges between 2 and 3 years (7, 8) and is associated with many GC-related side effects. Taken together, the disease and its symptoms, the chronic course and the treatment probably have an impact on the patients' quality of life (QoL), but few studies have been dedicated to this description. Medical consultations during the follow-up of a GCA patient are relatively time-limited and mostly focus on the evaluation of disease activity and treatment tolerance, both being mainly analyzed from a medical point of view.

In this study, we aimed to describe though a self-evaluation methodology, the impact of GCA and its treatments on the patients' QoL, including both physical and mental domains. Using validated scores and scales, we distinguished patients describing a modest impact of the disease and its treatment on their QoL from those with an important impact. From a comparison of these two groups, we sought to identify the factors that most significantly affected their QoL.

PATIENTS AND METHODS

Patients

All patients diagnosed with GCA and followed up in our department are included in a centralized database, and since 2015, data about each patient have been included prospectively.

From our centralized database, we retrieved the 100 last patients consecutively diagnosed with GCA in our department before 31 January 2020. In June 2020, we sent them a paper questionnaire with a stamped addressed envelope to favor returns. GCA diagnosis relied on usual criteria for the disease, including vasculitis demonstration either on the temporal artery by ultrasonography-Doppler or temporal artery biopsy and/or on the aorta and its branches by large-vessel imaging (9, 10). All patients had a regular follow-up in our department, even in the few years following GC discontinuation.

Two months after mailing the questionnaire, patients who did not respond were called on the phone. Missing information in the questionnaire was also retrieved by a systematic phone call to the patient.

The autoquestionnaire was joined to an information note explaining the objectives of the study and specifying that patients could refuse to participate. Patients who returned the questionnaire agreed to participate and gave a written informed consent.

This study was conducted in compliance with good clinical practices and the Declaration of Helsinki principles. At the time of this study, in accordance with French public health law (Art. L 1121-1-1, Art. L 1121-1-2), formal approval from an ethics committee was not required for this type of observational study. Our local ethics committee (Caen CLERS) confirmed the observational non-interventional nature of our work.

Items Included in the Questionnaire and Studied Parameters

The main objective of the questionnaire was to assess, according to the own point of view of the patients, with the possible contribution if necessary of their family caregiver, how the disease and its treatment have affected their daily life.

The questionnaire included three distinct parts. Part II and III of the questionnaire we sent to the patients is available as a **Supplementary Material**.

The first part, not reported in the present article, regards disease manifestations and clinical symptoms assessed by the patients themselves (with the possible help of their caregivers). The second part of the questionnaire regards the GC and their attributable effects. The patient-reported GC tolerance was assessed via questions that focused on eight main areas that we selected as potentially affected by the treatment: metabolic, cardiovascular, muscular, bone, cutaneous and pilar, ophthalmologic, infective, or neurocognitive and psychological complications. Patients were asked to check items in a list of predefined symptoms attributable to the disease or to GC, only if they appeared at GCA onset, during the follow-up or after GC introduction. Symptoms that preexisted before GCA were in theory not checked. In this second part, the GC-related side effects were analyzed according to the disease and treatment durations. The full description of this part is in another article.

The third part, which is reported in the present work, assessed the patients' QoL. Since GC-related side effects might influence the physical and mental disabilities of patients, we also included in this work some results of the second part.

We explored many potential physical and mental disabilities related to the disease and its treatment that might affect the patients' QoL. We thus developed close-ended questions (e.g., "At the disease onset, did you experience…?" or "Since the treatment start, did you …?"). Closed-ended questions were developed based upon the medical experience of the authors, who assess the abilities/disabilities of elderly patients daily, with the help of geriatricians. Moreover, some questions were retrieved from a literature review (11–16).

We also used the 12-item short form survey (SF-12) (QualityMetric Incorporated, License Number QM054800). The SF-12 survey explores physical, emotional and social health via assessment of physical activities, social activities, physical pain, general mental health, vitality and general health perception (17). In addition, the psychologic impact was assessed via the 30-item geriatric depression scale (GDS). The GDS added some items not explored in the SF-12 survey, especially regarding the consequences of an impaired mood. Moreover, this tool is especially appropriate to explore thymic states in elderly people.

In each patient, the SF-12 allowed us to calculate the physical score (PCS-12) and the mental score (MCS-12). A score $\geq$50

indicated no disability; 40-49: mild disability; 30–39: moderate disability; and <30: severe disability. We pooled together patients without and with mild disability on one side and those with moderate and severe disability on the other. Regarding the GDS, a score of 0–9 was normal, 10–19 suggested slight depression, and a score >19 was indicative of moderate to severe depression.

Based on the responses obtained in the second part of the questionnaire, we analyzed the specific impact of GC-related adverse events (AEs) on declared physical and mental disabilities.

Finally, we also asked patients to specify whether their physical autonomy, assessed via the ability to perform their usual daily activities, including walking, leaving the home, or climbing stairs, was affected since the disease diagnosis and its related treatment.

Data about baseline clinical manifestations and therapeutic management were retrieved via our centralized database.

Statistical Analysis

Categorical variables are expressed as numbers (%), and quantitative variables are expressed as medians [range]. To compare the two groups, categorical variables were analyzed using the Pearson or Fisher Chi-square test as appropriate, and quantitative variables were analyzed using Wilcoxon's rank-sum test.

Logistic regression was used to determine which factors were the most associated with moderate-to-severe physical or mental disability. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed for each factor in the univariate analysis and in the multivariate model with a backward stepwise approach using variables that reached $p < 0.2$ in univariate analyses.

Spearman correlation coefficients were calculated to assess the correlation between GDS and PCS-12 and between GDS and MCS-12.

The statistical analyses were computed using JMP 9.0.1 (SAS Institute Inc., Cary, NC, USA). A $p \leq 0.05$ defined statistical significance.

RESULTS

Among the 100 GCA patients solicited, 90 agreed to participate and sent back the completed questionnaire. The 10 patients who were not included were dead ($n = 3$), expressed a refusal to participate ($n = 1$) or did not send back the questionnaire ($n = 6$).

The 90 study participants were diagnosed with GCA from 2016 to early 2020, including 20 in 2016, 16 in 2017, 23 in 2018, 24 in 2019 and 7 in January 2020.

The median age of these 90 patients, among whom 71% were women, was 75 [60–94] years. The median follow-up since diagnosis was 20 [3–48] months, and 52 (58%) patients still received GC when completing the questionnaire. At the time of questionnaire completion, the overall GC median duration for the whole cohort, including patients who continued, was 17 [3–48] months. Twenty-nine (32%) patients received an immunosuppressant, methotrexate for 14 and tocilizumab for 15.

TABLE 1 | Comparison of GCA patients according to the felt severity of physical disability assessed by the SF-12 survey.

	None-to-slight physical disability ($n = 49$)	Moderate-to-severe physical disability ($n = 41$)	*P*
Demographics			
Age ≥80	11 (22)	21 (51)	0.005
Female	33 (67)	31 (76)	0.39
Cardiovascular risk factors before GCA			
≥2 cardiovascular risk factors	18 (37)	13 (32)	0.61
Coronaropathy	0	6 (15)	0.006
Any stroke before GCA	0	1 (2)	0.27
GCA characteristics at diagnosis			
Large-vessel vasculitis	14/47 (30)	14/40 (35)	0.60
Any cranial sign	40 (82)	31 (76)	0.49
Ophthalmologic sign	16 (33)	13 (32)	0.92
Uni- or bi-lateral blindness	4 (18)	4 (31)	0.39
Polymyalgia rheumatica	21 (43)	14 (34)	0.40
GCA treatments and course			
GC discontinuation at last follow-up	17 (35)	21 (51)	0.11
GC duration in all patients	17 [6–48]	19 [6–44]	0.24
GC duration of >18 months	19 (39)	21 (51)	0.24
Use of immune-suppressants	15 (31)	14 (34)	0.72
Any disease relapse	25 (51)	24 (58)	0.48
Total follow-up	17 [6–48]	21 [6–50]	0.11
Follow-up for GCA lasting >2 years	28 (57)	31 (76)	0.07
Felt adverse events attributable to GC	39 (80)	34 (83)	0.69
Cardiovascular changes	15 (31)	12 (29)	0.89
Any metabolic complications	23 (47)	21 (51)	0.69
Diabetes mellitus	6 (12)	12 (29)	0.04
Weight gain	20 (41)	16 (39)	0.86
Muscle mass and strength reduction	27 (55)	36 (88)	0.0007
Cognitive and psychologic changes	44 (90)	37 (90)	0.13
Memory loss	15 (30)	21 (51)	0.047
Depressive mood	15 (31)	20 (49)	0.08
Exalted mood	16 (33)	10 (24)	0.39
Insomnia	36 (73)	29 (70)	0.77
Irritability	25 (51)	17 (41)	0.37
Osteoporotic fractures	3 (6)	5 (12)	0.31
Cutaneous and hairiness changes	30 (61)	33 (80)	0.047
Any infections requiring treatment	9 (18)	14 (34)	0.09
Any visual change	15 (31)	23 (56)	0.01
Cataract	14 (29)	21 (51)	0.03
Persisting articular pain	24 (49)	30 (73)	0.02
Reduction of physical autonomy	23 (47)	34 (83)	0.0004
Need some help in daily activities	4 (8)	13 (32)	0.005
Mechanical fall	10 (20)	9 (22)	0.86
Walking difficulties	10 (20)	27 (66)	<0.0001

Values are numbers (%) or medians [range].
GCA, giant-cell arteritis; GC, glucocorticoids.

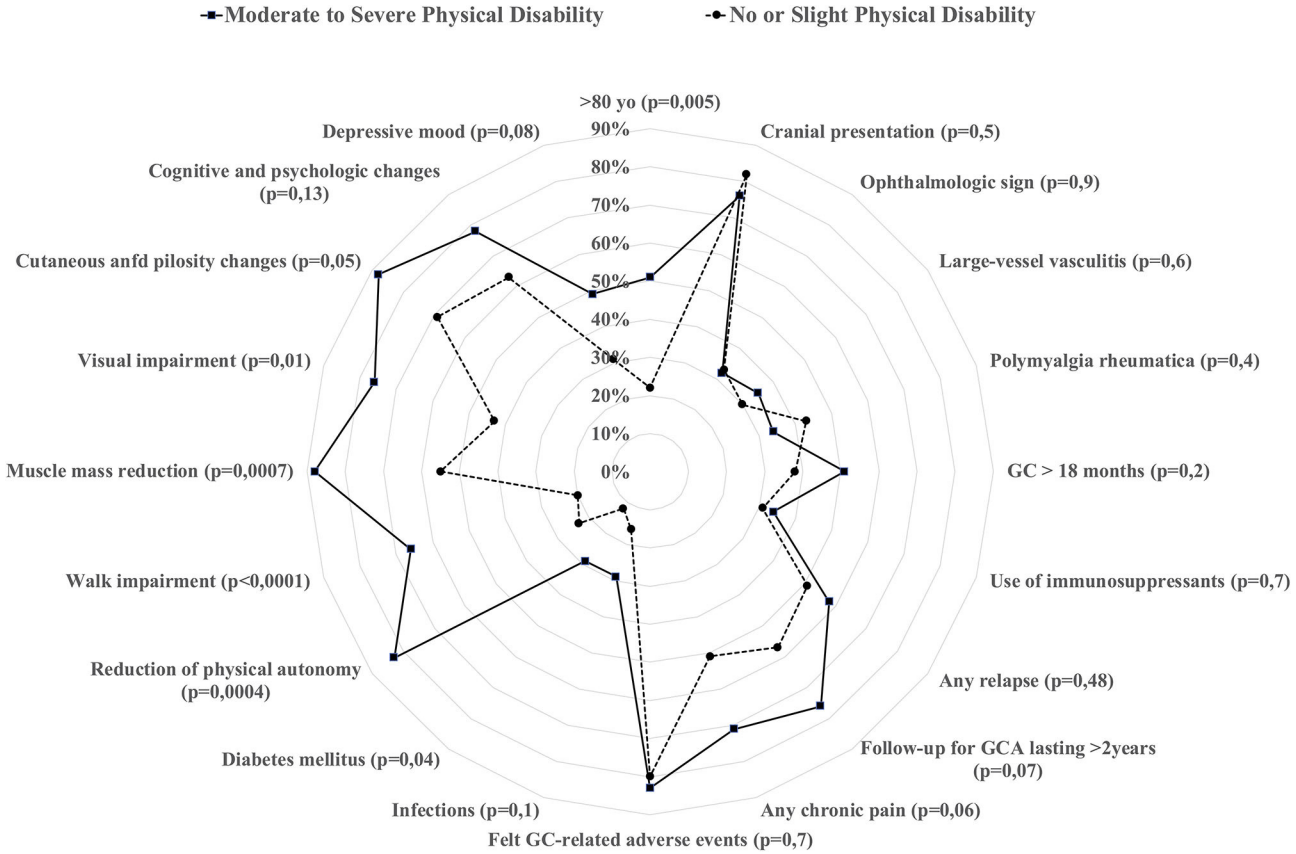

FIGURE 1 | Comparison of different characteristics at GCA baseline and during follow-up according to whether the patients stated they suffered from moderate-to-severe physical disability (calculated through the SF-12 survey).

Factors Associated With Moderate-to-Severe Physical Disability

According to the SF-12, the median physical score was 41 [21–57]. Twenty-two (24%) patients had a score >50, i.e., did not report any physical disability; 27 (30%) reported a score between 40 and 49, i.e., expressed a mild physical disability; 28 (31%) reported a score between 30 and 39, i.e., a moderate physical disability; and 13 (14%) reported a score <30, indicative of a severe physical disability. Altogether, 49 (54%) patients expressed no or slight physical disability, whereas 41 others (46%) described moderate-to-severe physical disability. We compared these 2 groups in **Table 1** and **Figure 1**.

At baseline, patients with moderate-to-severe physical disability more frequently were >80 years of age (51 vs. 22%, $p = 0.005$) and had coronaropathies (15% vs. none in the other group, $p = 0.006$). Although the rate of GC-related AEs was not different between the two groups, patients with moderate-to-severe physical disability developed more diabetes (29 vs. 12%, $p = 0.04$), more muscle and strength reduction (88 vs. 55%, $p = 0.0007$), and more visual changes (56 vs. 31%, $p = 0.01$). Patients with moderate-to-severe physical disability also reported reduced autonomy (83 vs. 47%, $p = 0.0004$), especially walking impairment (66 vs. 20%, $p < 0.0001$).

In **Table 2**, we identified through logistic regression the factors most associated with moderate-to-severe physical disability. Walk difficulties ($OR = 8.42$ [95% CI, 2.98–26.82], $p < 0.0001$), muscle mass and strength reduction (OR = 4.38 [1.3–16.31], $p = 0.01$) and age >80 years (OR = 4.21 [1.44–13.61], $p = 0.008$) were the 3 factors with the most negative impact on physical disability.

Factors Associated With Moderate-to-Severe Mental Disability

According to the SF-12, the median mental score was 46 [22–62]. Thirty-tree (37%) patients had a score ≥50, i.e., did not report any mental disability; 27 (30%) reported a score between 40 and 49, i.e., mild mental disability; 20 (22%) reported a score between 30 and 39, i.e., moderate mental disability; and 10 (11%) reported a score <30, indicative of a severe mental disability. Altogether, 60 (67%) had no or slight mental disability, and 30 (33%) described moderate-to-severe mental disability. We compared these 2 groups in **Table 3** and **Figure 2**.

At baseline, patients who reported moderate-to-severe mental disability more frequently suffered from GCA-related ophthalmologic signs (47 vs. 25%, $p = 0.04$). They also reported more felt GC-related AEs (97 vs. 73%, $p = 0.008$), especially cardiovascular changes (47 vs. 22%, $p = 0.01$), muscle mass

TABLE 2 | Factors associated with moderate-to-severe physical disability in univariate and multivariate models.

	Univariate OR, 95% CI	*P*	Multivariate OR, 95% CI	*p*
Age >80	3.62 [1.49–9.26]	0.004	4.21 [1.44–13.61]	0.008
GC discontinuation	1.97 [0.85–4.68]	0.11		
GC duration >12 months	1.88 [0.78–4.72]	0.16		
GCA >2 years	2.32 [0.95–5.95]	0.06		
Diabetes mellitus	2.97 [1.03–9.36]	0.04		
Cutaneous and hairiness changes	2.61 [1.02–7.15]	0.04		
Muscle mass and strength reduction	5.87 [2.1–19.33]	0.0005	4.38 [1.37–16.31]	0.01
Persisting articular pain	2.32 [0.98–5.70]	0.06		
Memory loss	2.38 [1.01–5.73]	0.05		
Depressive mood	2.15 [0.92–5.19]	0.08		
Any infections requiring treatment	2.30 [0.88–6.26]	0.09		
Any visual change	2.90 [1.23–7.02]	0.01		
Walking difficulties	7.52 [3–20.23]	<0.0001	8.42 [2.98–26.82]	<0.0001

Odds ratios (ORs) and 95% confidence intervals (CIs).
GCA, giant cell arteritis; GC, glucocorticoids.

and strength reduction (93 vs. 58%, $p = 0.0006$), or depressive mood (73 vs. 13%, $p < 0.0001$). They also more frequently reported a reduction in their physical autonomy (80 vs. 55%, $p = 0.02$). Regarding therapeutic management, the GC durations ($p = 0.81$) were not different in either group, nor was the rate of relapse ($p = 0.55$). However, patients who reported moderate-to-severe mental disability more frequently received an immunosuppressant (47 vs. 25%, $p = 0.04$). Among the 29 patients who received an immunosuppressant, 7/14 (50%) who received methotrexate vs. 7/15 (47%) who received tocilizumab described moderate-to-severe mental disability ($p = 1$).

In **Table 4**, we identified via logistic regression the factors most associated with moderate-to-severe mental disability. Depressive mood (OR = 11.05 [95% CI, 3.78–37.11], $p < 0.0001$), felt GC-related AEs (OR = 10.54 [1.65–213.1], $p = 0.01$) and the use of an immunosuppressant (OR = 3.50 [1.14–11.87], $p = 0.03$) were the 3 factors with the most negative impact on mental disability.

Psychologic Impact Assessed via the 15-Item Geriatric Depression Scale

Among the 90 patients, 16 (18%) did not have any sign of mood disorder, 72 (80%) had slight depression and 2 (2%) had moderate-to-severe depression. The Pearson correlation with the associated p-value was calculated between the GDS and the PCS-12 and the GDS and the MCS-12. There was a statistically significant negative correlation between GDS and the physical and/or mental disability scores (GDS and PCS-12: $r = -0.33$, $p = 0.0013$; GDS and MCS-12: $r = -0.36$, $p = 0.0005$).

TABLE 3 | Comparison of GCA patients according to the felt severity of mental disability as assessed by the SF-12 survey.

	None-to-slight mental disability ($n = 60$)	Moderate-to-severe mental disability ($n = 30$)	*p*
Demographics			
Age >80	18 (30)	14 (47)	0.12
Female	42 (70)	22 (73)	0.74
Cardiovascular risk factors before GCA			
>2 cardiovascular risk factors	21 (35)	10 (33)	0.88
Coronaropathy	3 (5)	3 (10)	0.37
Any stroke before GCA	0	1 (3)	0.16
GCA characteristics at diagnosis			
Large-vessel vasculitis	17 (28)	11 (41)	0.25
Any cranial sign	46 (77)	25 (83)	0.47
Ophthalmologic sign	15 (25)	14 (47)	0.04
Uni- or bi-lateral blindness	3 (13)	5 (42)	0.06
Polymyalgia rheumatica	22 (37)	13 (43)	0.54
GCA treatments and course			
GC discontinuation at last follow-up	24 (40)	14 (47)	0.55
GC duration in all patients	17 [6–48]	18 [6–44]	0.81
Total follow-up	19 [6–50]	24 [6–47]	0.33
GC duration of >18 months	27 (45)	13 (43)	0.88
Use of immunosuppressants	15 (25)	14 (47)	0.04
Any disease relapse	34 (57)	15 (50)	0.55
Follow-up for GCA lasting >2 years	21 (35)	10 (33)	0.88
Felt adverse events attributable to GC	44 (73)	29 (97)	0.008
Cardiovascular changes	13 (22)	14 (47)	0.01
Any metabolic complications	28 (47)	16 (53)	0.55
Diabetes mellitus	10 (17)	8 (27)	0.26
Weight gain	23 (38)	13 (43)	0.65
Muscle mass and strength reduction	35 (58)	28 (93)	0.0006
Cognitive and psychologic changes	51 (85)	30 (100)	0.03
Memory loss	22 (37)	14 (47)	0.36
Depressive mood	13 (22)	22 (73)	<0.0001
Exalted mood	13 (22)	13 (43)	0.03
Insomnia	41 (68)	24 (80)	0.24
Irritability	24 (40)	18 (60)	0.07
Osteoporotic fractures	4 (7)	4 (13)	0.29
Cutaneous and hairiness changes	40 (67)	23 (77)	0.33
Any infections requiring treatment	12 (20)	11 (37)	0.09
Any visual change	26 (43)	12 (40)	0.76
Persisting articular pain	37 (62)	17 (57)	0.65
Reduction of physical autonomy	33 (55)	24 (80)	0.02
Need some help in daily activities	10 (17)	7 (23)	0.45
Mechanical fall	11 (18)	8 (27)	0.36
Walk difficulties	21 (35)	16 (53)	0.1

Values are numbers (%) or medians [range].
GCA, giant-cell arteritis; GC, glucocorticoids.

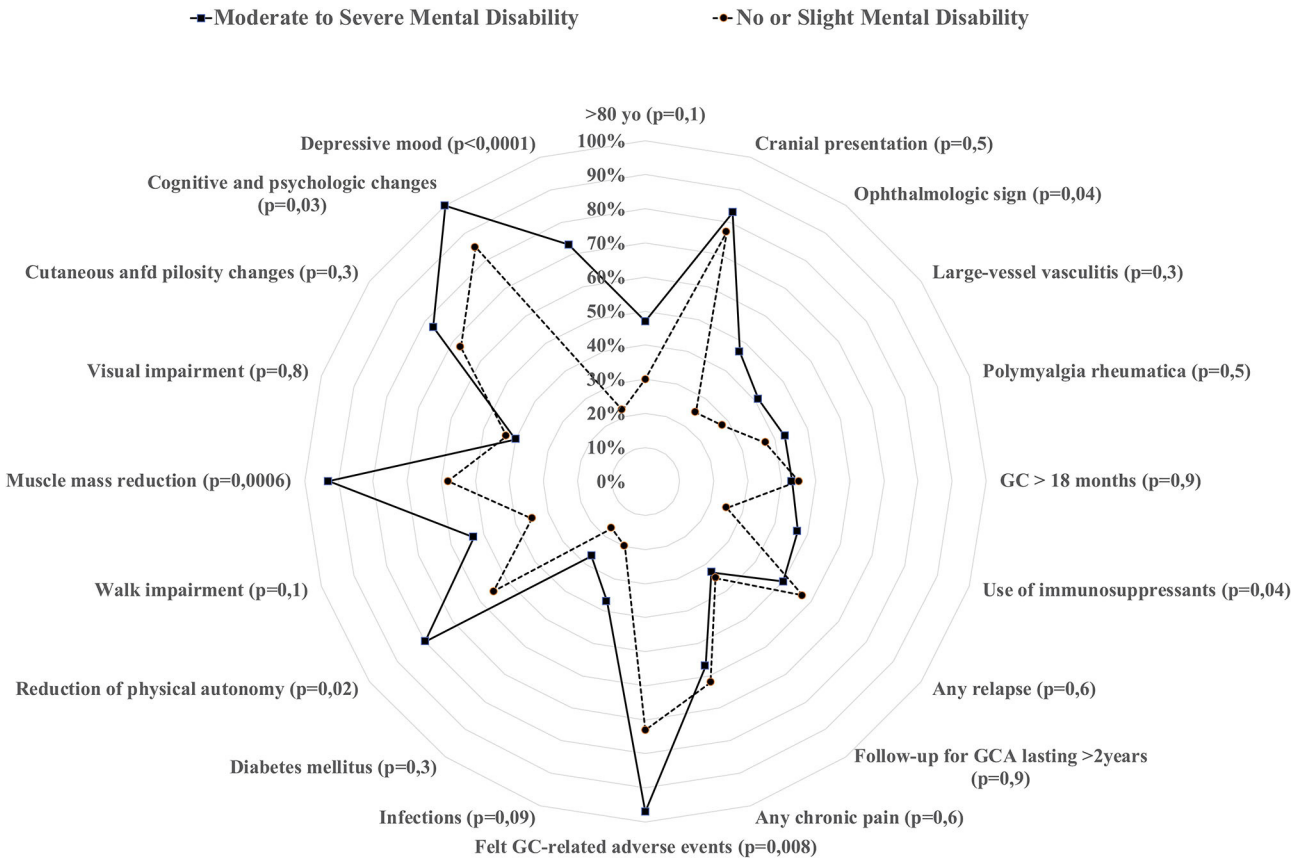

FIGURE 2 | Comparison of different characteristics at GCA baseline and during follow-up according to whether the patients stated they suffered from moderate-to-severe mental disability (calculated through the SF-12 survey).

DISCUSSION

The impact of the chronic course of GCA and its prolonged treatment on patients' QoL has been poorly analyzed. In the present study, we showed that approximately one-third to half of patients reported a physical and/or mental disability attributable to GCA and its treatment in the months or years following diagnosis. We observed that the described physical disabilities were not directly associated with GCA manifestations or with treatment management. Conversely, reductions in muscular mass and strength, walk impairment and visual deterioration were strongly associated with the severity of physical disability. However, even though these comorbidities are potentially linked or worsened by GC use, they should also be the consequence of natural aging, which is emphasized by the older age of patients with severe physical disability. Walking difficulties, and more extensively impairment of mobility, are reported in a few GCA studies and lead to a reduction of the physical autonomy and the ability to ensure daily activities such as self-care, dressing, washing, or shopping, which is concordant with our study (11, 12). Other studies have reported the negative impact of GCA and its treatment on some patients' ability to work, practice usual hobbies or leisure activities (12, 13). Altogether, these findings suggest paying particular attention to maintaining muscular autonomy and physical activities in the oldest patients, and encourage us to propose muscle reinforcement programs for these patients.

In accordance with others (12, 14, 15), our study showed that mental disability was worsened by GCA-related ophthalmologic impairment. Interestingly, patients also reported the negative mental impact of treatments, especially due to GC and immune-suppressants. In some of the studies where GCA patients were directly interviewed, they reported that GC increased their stress and anxiety, possibly leading to social isolation (12, 15). The mental assessment via the SF-12 survey and the GDS indicated that >80% of patients showed some signs of mood disorders. Other studies confirmed reduced self-esteem in GCA patients with a negative perception of their health and the feeling of not living a normal life (12, 13).

Many other factors, independent of GCA and its treatment, might be related to this thymic decline. However, this observation suggests the importance of thymic evaluation in GCA patients.

Based on our results, two main points should be highlighted. First, regardless of the disease status and its treatment, our patients showed an altered QoL, especially when aged >80. Although the exact role of GCA and its treatment cannot be precisely assessed in a global QoL evaluation, some targetable and measurable clinical and social parameters can be routinely

TABLE 4 | Factors associated with moderate-to-severe mental disability in univariate and multivariate models.

	Univariate OR, 95% CI	*P*	Multivariate OR, 95% CI	*p*
Age >80	2 [0.82–5.09]	0.12		
Ophthalmologic sign at diagnosis	2.63 [1.04-6.71]	0.04		
Use of immunosuppressants	2.53 [1.02–6.37]	0.04	3.50 [1.14–11.87]	0.03
Felt adverse events attributable to GC	10.5 [1.98–195.4]	0.003	10.54 [1.65–213.1]	0.01
Cardiovascular complications	3.16 [1.24–8.28]	0.02		
Reduction of physical autonomy	3.27 [1.23–9.88]	0.02		
Walking difficulties	2.12 [0.87–5.25]	0.1		
Muscle mass and strength reduction	10 [2.66–65.5]	0.0002		
Cognitive and psychologic changes	6 [1.85–27.09]	0.002		
Depressive mood	9.94 [3.74–28.96]	<0.0001	11.05 [3.78–37.11]	<0.0001
Exalted mood	2.76 [1.07–7.24]	0.04		
Irritability	2.25 [0.93–5.62]	0.07		
Any infections requiring treatment	2.32 [0.87–6.20]	0.09		

Odds ratios (ORs) and 95% confidence intervals (CIs).
GCA, giant cell arteritis; GC, glucocorticoids.

checked during follow-up, such as physical autonomy or muscle mass maintenance.

Even though not directly assessed in this study, optimal management of GC to reduce AEs should remain a priority. Additionally, this study emphasizes the need for patient-reported outcome measures to evaluate the GC effect, which is in accordance with a recent study (16). Therefore, different international initiatives are planned to improve outcome measurement, especially through OMERACT programs (16–19).

The second main point regards the multidisciplinary approach required to correctly manage GCA patients. In addition to disease evaluation and treatment management, physicians should integrate the geriatric dimension of some GCA patients. Other actors, such as geriatricians, psychologists or psychiatrists, physiotherapists, in-home caregivers and therapeutic education professionals should be integrated into the care pathway of GCA patients.

Although our study is one of the few reporting patient outcomes through a self-evaluation in GCA, some points should be acknowledged and might reduce the validity of our observations. First, in the absence of a control group, the patients reported some symptoms that they attributed to the disease or its treatment, but no firm confirmation could be made. Although we observed an impaired QoL in many patients, we cannot conclude that their QoL was more impaired than other aged-matched healthy people. However, the first goal of this study was to provide a descriptive picture of the medical and social impacts of the disease and its treatment in the daily lives of GCA patients. Given the methodology used, each patient completed the questionnaire at different times of their disease and treatment, which can influence some results. However, we did not find any association between the disease or treatment durations and the disabilities. In addition to validated scales (SF-12, GDS), some of the questions addressed to patients were developed from our own experience and were not all replicated in other studies. The reduction of physical autonomy or the impact of muscle mass reduction can be linked to other important factors, such as aging, and may be independent of GCA and treatment. Second, some recall biases are likely. Given the old age of some of the patients and the possible cognitive-associated troubles, some symptoms should have been added or forgotten; however, the potential help of familial caregivers should have reduced this bias. The impact of treatment only focused on GC, but some patients also received immune-suppressants that can add some AEs, which were not assessed in this study. Immuno-suppressants probably have an impact since we showed that patients with a concomitant immunosuppressant had a more important mental disability, regardless of the type of immunosuppressant, i.e., methotrexate or tocilizumab.

To conclude, our study shows that GCA patients' QoL is frequently impaired by the disease or its treatment, regardless of the intrinsic favorable benefit of the latter. Important reported factors reflecting a severe disability, such as walking difficulties, muscle mass reduction, and glucocorticoid-related adverse events, were revealed by this study and are modifiable by medical and home care. Further studies, especially with a control group, are required to confirm our results and reinforce knowledge about disease-modifiable factors that affect patients' QoL.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by CLERS-CAEN. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HdB designed the study, analyzed the data, and wrote the manuscript. HdB, CB, AD, JB, NMS, GM, AN, AL, PC, SG, AS, SD, and AA collected the data and critically revised and edited the manuscript. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.777310/full#supplementary-material

REFERENCES

1. Salvarani C, Cantini F, Hunder GG. Polymyalgia rheumatica and giant-cell arteritis. *Lancet*. (2008) 372:234–45. doi: 10.1016/S0140-6736(08)61077-6
2. Albrecht K, Huscher D, Buttgereit F, Aringer M, Hoese G, Ochs W, et al. Long-term glucocorticoid treatment in patients with polymyalgia rheumatica, giant cell arteritis, or both diseases: results from a national rheumatology database. *Rheumatol Int*. (2018) 38:569–77. doi: 10.1007/s00296-017-3874-3
3. Buttgereit F, Matteson EL, Dejaco C, Dasgupta B. Prevention of glucocorticoid morbidity in giant cell arteritis. *Rheumatology*. (2018) 57:ii11–21. doi: 10.1093/rheumatology/kex459
4. Mainbourg S, Addario A, Samson M, Puechal X, Francois M, Durupt S, et al. Prevalence of giant cell arteritis relapse in patients treated with glucocorticoids: a meta-analysis. *Arthritis Care Res.* (2020) 72:838–49. doi: 10.1002/acr.23901
5. Wilson JC, Sarsour K, Collinson N, Tuckwell K, Musselman D, Klearman M, et al. Incidence of outcomes potentially associated with corticosteroid therapy in patients with giant cell arteritis. *Semin Arthritis Rheum*. (2017) 46:650–6. doi: 10.1016/j.semarthrit.2016.10.001
6. Therkildsen P, de Thurah A, Hansen IT, Norgaard M, Nielsen BD, Hauge EM. Giant cell arteritis: a nationwide, population-based cohort study on incidence, diagnostic imaging, and glucocorticoid treatment. *Semin Arthritis Rheum*. (2021) 51:360–6. doi: 10.1016/j.semarthrit.2021.01.007
7. Bienvenu B, Ly KH, Lambert M, Agard C, Andre M, Benhamou Y, et al. Management of giant cell arteritis: recommendations of the French Study Group for Large Vessel Vasculitis (GEFA). *Rev Med Interne.* (2016) 37:154–65. doi: 10.1016/j.revmed.2015.12.016
8. Hellmich B, Agueda A, Monti S, Buttgereit F, de Boysson H, Brouwer E, et al. 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. *Ann Rheum Dis*. (2020) 79:19–30. doi: 10.1136/annrheumdis-2019-215672
9. Hunder GG, Bloch DA, Michel BA, Stevens MB, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. *Arthritis Rheum.* (1990) 33:1122–8. doi: 10.1002/art.1780330810
10. 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) 377:317–28. doi: 10.1056/NEJMoa1613849
11. Jobard S, Magnant J, Blasco H, Ferreira-Maldent N, Griffoul I, Diot E, et al. Quality of life of patients treated for giant cell arteritis: a case-control study. *Clin Rheumatol.* (2017) 36:2055–62. doi: 10.1007/s10067-017-3619-4
12. Robson JC, Alemida C, Dawson J, Bromhead A, Dures E, Guly C, et al. Patient perceptions of health-related quality of life in giant cell arteritis: international development of a disease-specific patient-reported outcome measure. *Rheumatology*. (2021) 60:4671–80. doi: 10.1093/rheumatology/keab076
13. Liddle J, Bartlam R, Mallen CD, Mackie SL, Prior JA, Helliwell T, et al. What is the impact of giant cell arteritis on patients' lives? A UK qualitative study. *BMJ Open.* (2017) 7:e017073 doi: 10.1136/bmjopen-2017-017073
14. Hellmann DB, Uhlfelder ML, Stone JH, Jenckes MW, Cid MC, Guillevin L, et al. Domains of health-related quality of life important to patients with giant cell arteritis. *Arthritis Rheum.* (2003) 49:819–25. doi: 10.1002/art.11464
15. Kupersmith MJ, Speira R, Langer R, Richmond M, Peterson M, Speira H, et al. Visual function and quality of life among patients with giant cell. (temporal) arteritis. *J Neuroophthalmol.* (2001) 21:266–73. doi: 10.1097/00041327-200112000-00008
16. Black RJ, Robson JC, Goodman SM, Hoon E, Lai LYH. A patient-reported outcome measure for effect of glucocorticoid therapy in adults with inflammatory diseases is needed: report from the OMERACT 2016 Special Interest Group. *J Rheumatol.* (2017) 44:1754–8. doi: 10.3899/jrheum.161083
17. Gandek B, Ware JE, Aaronson NK, Apolone G, Bjorner JB, Brazier JE, et al. Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: results from the IQOLA project. International Quality of Life Assessment. *J Clin Epidemiol.* (1998) 51:1171–8. doi: 10.1016/S0895-4356(98)00109-7
18. Cheah JTL, Black RJ, Robson JC, Navarro-Millan IY, Young SR, Richards P, et al. Toward a core domain set for glucocorticoid impact in inflammatory rheumatic diseases: the OMERACT 2018 Glucocorticoid Impact Working Group. *J Rheumatol.* (2019) 46:1179–82. doi: 10.3899/jrheum.181082
19. Flurey CA, Tugwell PS, Black RJ, Halls S, Page MJ, Robson JC, et al. The OMERACT emerging leaders program: the good, the bad, and the future. *J Rheumatol.* (2019) 46:1047–52. doi: 10.3899/jrheum.181126

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ORIGINAL RESEARCH
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Presentation and Real-World Management of Giant Cell Arteritis (Artemis Study)

Alfred Mahr[1], Eric Hachulla[2], Hubert de Boysson[3], Nassim Guerroui[4], Emmanuel Héron[5], Stéphane Vinzio[6], Jonathan Broner[7], François-Xavier Lapébie[8], Martin Michaud[9], Laurent Sailler[10], Thierry Zenone[11], Mohamed Djerad[12], Mathieu Jouvray[13], Emilie Shipley[14], Nathalie Tieulie[15], Guillaume Armengol[16], Bastien Bouldoires[17], Jean-Francois Viallard[18], Isabelle Idier[19], Marc Paccalin[20] and Valérie Devauchelle-Pensec[21]*

[1] Department of Internal Medicine, University Hospital Paris (AP-HP, Saint Louis), Paris, France, [2] Department of Internal Medicine, Lille University Hospital, Lille, France, [3] Department of Internal Medicine, Caen University Hospital, Caen, France, [4] Department of Rheumatology, European Hospital of Marseille, Marseille, France, [5] Department of Internal Medicine, Hospital Quinze-Vingts, Internal Medicine, Paris, France, [6] Department of Internal Medicine, Groupe Hospitalier Mutualiste de Grenoble, Grenoble, France, [7] Department of Internal Medicine, University Hospital Centre Nimes, Nimes, France, [8] Department of Internal Medicine, University Hospital Centre Toulouse, Toulouse, France, [9] Department of Internal Medicine, Hopital Joseph Ducuing Toulouse, Toulouse, France, [10] Department of Internal Medicine, University Hospital of Toulouse, Toulouse, France, [11] Department of Internal Medicine, General Hospital of Valence, Valence, France, [12] Department of Internal Medicine, General Hospital of Nevers, Nevers, France, [13] Department of Internal Medicine, General Hospital of Arras, Arras, France, [14] Department of Rheumatology, General Hospital of Dax, Dax, France, [15] Department of Rheumatology, University Hospital of Nice, Nice, France, [16] Department of Internal Medicine, Rouen University Hospital, Rouen, France, [17] Department of Internal Medicine, Civil Hospital of Colmar, Colmar, France, [18] Department of Internal Medicine, University Hospital of Bordeaux, Bordeaux, France, [19] Medical Affairs, Chugai Pharma France, Paris La Défense, Paris, France, [20] Department of Internal Medicine, University Hospital of Poitiers, Poitiers, France, [21] Rheumatology Department, University Hospital La Cavale Blanche, Brest, France

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Edited by:
Peter Mandl,
Medical University of Vienna, Austria

Reviewed by:
Vidya Limaye,
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Fatma Alibaz-Oner,
Marmara University, Turkey

***Correspondence:**
Alfred Mahr
Alfred.Mahr@kssg.ch

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Background: Few studies of daily practice for patients with giant cell arteritis (GCA) are available. This French study aimed to describe the characteristics and management of GCA in a real-life setting.

Methods: Cross-sectional, non-interventional, multicenter study of patients ≥50 years old who consulted hospital-based specialists for GCA and were under treatment. Patient characteristics and journey, diagnostic methods and treatments were collected. Descriptive analyses were performed.

Results: In total, 306 patients (67% females, mean age 74 ± 8 years old) were recruited by 69 physicians (internists: 85%, rheumatologists: 15%); 13% of patients had newly diagnosed GCA (diagnosis-to-visit interval <6 weeks). Overall median disease duration was 13 months (interquartile range 5–26). Most patients were referred by general practitioners (56%), then ophthalmologists (10%) and neurologists (7%). Most common comorbidities were hypertension (46%), psychiatric disorders (10%), dyslipidemia (12%), diabetes (9%), and osteoporosis (6%). Initial GCA presentations included cranial symptoms (89%), constitutional symptoms (74%), polymyalgia rheumatica (48%), and/or other extra-cranial manifestations (35%). Overall, 85, 31, 26, and 30% of patients underwent temporal artery biopsy, high-resolution temporal artery Doppler ultrasonography, ^{18}FDG-PET, and aortic angio-CT, respectively. All patients received

glucocorticoids, which were ongoing for 89%; 29% also received adjunct medication(s) (methotrexate: 19%, tocilizumab: 15%). A total of 40% had relapse(s); the median time to the first relapse was 10 months. Also, 37% had comorbidity(ies) related to or aggravated by glucocorticoids therapy.

Conclusion: This large observational study provides insight into current medical practices for GCA. More than one third of patients had comorbidities related to glucocorticoid therapy for a median disease duration of 13 months. Methotrexate and tocilizumab were the most common adjunct medications.

Keywords: giant cell arteritis, phenotype [mesh], management - healthcare, observational, glucocorticoids (GCs), methotrexate, tocilizumab

KEY MESSAGES

- Large-vessel giant cell arteritis (i.e., large-vessel involvement only) is rare (5%).
- 37% of patients experienced at least one comorbidity related to or aggravated by glucocorticoids treatment.
- One third of patients received adjunctive medication(s) (methotrexate, tocilizumab).

INTRODUCTION

Giant cell arteritis (GCA) is an inflammatory vasculopathy and the most frequent systemic vasculitis in Western countries. GCA involves large- and medium-sized arteries, predominantly the extracranial branches of the carotid arteries and the subclavian and axillary branches of the aorta (1). GCA affects older people and women more than men, with an incidence of 10 to 20/100,000 people ≥50 years old in Europe (2).

In addition to the classic cranial arteritis features, GCA includes polymyalgia rheumatica (PMR), other extra-cranial manifestations, and/or constitutional symptoms (3, 4). Apart from upper- or lower-limb claudication, large-vessel GCA (LV-GCA) might be asymptomatic. All these presentations may coincide together, occur as independent clinical subsets, or overlap. Visual ischemic complications, stroke, and aortic aneurysm or dissection are the most feared complications.

The diagnostic methods and recommended management of GCA have recently evolved. For a few decades, temporal artery biopsy (TAB) has been considered the gold standard for GCA diagnosis, and it often remains the first-intention test to propose, notably in France (5, 6). However, less invasive vascular imaging modalities are increasingly being used to study the cranial or extracranial arteries, including aorta inflammation. In this context, recommendations of the European League against Rheumatism (EULAR) on imaging in LV-GCA (7) were updated in 2018. In particular, EULAR recommendations now promote ultrasonography as the first choice for diagnosis in predominantly cranial GCA, with an additional investigation, including TAB, when the diagnosis is still in question.

Glucocorticoids (GCs) are the treatment of choice for GCA and should be initiated immediately with suspected GCA to induce remission and prevent complications (8); however, relapses are common, up to 40% (6), when the GC dose is tapered, which leads to prolonged or repeated oral treatment with risk of adverse effects (9). According to recent European or French recommendations (6, 8), tocilizumab (TCZ) (10, 11) or alternatively methotrexate (MTX) can be combined with GCs to reduce the GC toxicity. Other potential adjunct therapies (immunosuppressants and biologics) lack convincing results (6).

We do not know to what extent recent recommendations on the diagnosis and treatment of GCA are implemented in clinical practice. In France, first responses have been provided in a recent study based on national administrative health insurance claims data (12): TAB was used in 51% of the patients, and MTX was the most prescribed GC-sparing agent (12%). However, we have limited data on patients' comorbidities, clinical presentation and forms, cumulative doses for GCs as well as the use of imaging techniques for GCA diagnosis.

The aim of the study was to provide an overview of GCA, specifically the characteristics and management, in a real-life setting.

MATERIALS AND METHODS

Study Design

ARTEMIS is a cross-sectional, non-interventional, multicenter French study conducted among hospital-based internists and rheumatologists. All 2,676 eligible specialists, hospital-based internists and rheumatologists in a national independent French database were invited to participate in the study. Each specialist who agreed to participate was requested to include, consecutively during the inclusion period, a maximum of 10 patients to limit a potential center effect. According to French legislation regarding non-interventional studies, the ARTEMIS protocol (ClinicalTrials.gov NCT03658889) was approved by the ethics committee (authorization no: 2018-A00841-54. 2-18-37), which guarantees confidentiality to the participants. All patients were informed with an information document completed by investigators about the study before enrolment and had no objection to sharing their data (written consent is not mandatory for non-interventional studies according to French legislation: CNIL1818705X, No 2018-15). This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments.

Patients and Data Collection

Eligible patients were adults ≥50 years old who were seen as in- or outpatients for a new or previously diagnosed GCA. The diagnosis of GCA was according to the investigator's judgment regardless of the specific criteria used. In addition, patients had to be under GCA treatment at the inclusion visit and have no objection to participate in the study. Patients participating in an interventional study were excluded.

At the study visit, specialists collected the following information by using an electronic Case Report Form: patient journey, GCA characteristics, diagnostic methods, GCA treatments and comorbidities related to or aggravated by GCs. GCA activity was assessed by using a 100-mm visual analog scale (VAS) completed by patients and physicians.

Statistics

No formal sample size was calculated for this non-interventional study. However, from a previous study of GCA patients (database analysis of the *Echantillon Généraliste des Bénéficiaires*), there are 2,300 incident patients/year in France (12). Therefore, the inclusion of 300 incident and prevalent patients during the planned 5-month recruitment period seemed realistic.

Descriptive analyses were performed. Study variables were assessed with mean ± standard deviation (SD) or median [interquartile range (IQR)] for continuous variables and number (%) for categorical variables. Missing values were not replaced. Statistical analysis involved using SAS 9.3 (SAS Institute, Cary, NC, USA).

The GCA diagnosis was considered early, standard, or late when the time between first GCA symptoms and diagnosis was <1 month, 1–3 months, or >3 months, respectively. Analysis of GCA data was according to the diagnosis-to-visit interval (incident disease: <6 weeks, prevalent disease: ≥6 weeks). Cranial involvement included headaches, temporal artery abnormalities, jaw claudication, scalp tenderness, visual symptoms, and stroke and transient ischemic attack(s); LV involvement included aortic aneurysm or dilatation, aortitis and/or involvement of aortic branch(s) on imaging, claudication of a limb, sign(s) of subclavian stenosis.

RESULTS

Participant Physicians and Patient Disposition

Of the 2,676 French eligible specialists invited to participate in the study, 69 from 53 centers accepted and included at least one eligible patient. Participating specialists were mainly working in a university hospital (39/69, 56.5%) or a general hospital (30/69, 43.5%).

Of the 308 patients included from August to November 2018 by 69 hospital-based specialists (internists: 84%, rheumatologists: 15%, geriatricians: 1%), 306 fulfilled all the selection criteria. Two patients without GCA treatment at the study visit were excluded.

Characteristics of Patients

The characteristics of the patients are detailed in **Table 1**. The mean age of patients (67% female) was 74.0 ± 7.9 years at the study visit. Most (83%) patients had comorbidity(ies) before GCA was diagnosed, mainly hypertension, dyslipidemia, diabetes, and/or osteoporosis. Eye disorders (cataract and glaucoma) were reported in 10% of patients.

At the study visit, most patients (79%) consulted the participant hospital-based specialists as outpatients, and most (87%) had prevalent disease (diagnosis-to-visit interval >6 months). Various physicians referred the patients to participant

TABLE 1 | Characteristics of patients.

Parameter	Number of analyzed patients	Total *(N = 306)*
Demographics at inclusion		
Age (years), mean ± SD	306	74.0 ± 7.9
Age ≥70 years, *n* (%)	306	222 (72.5)
Female sex, *n* (%)	306	206 (65.3)
Body mass index at diagnosis (kg/m²)	292	
Mean ± SD		24.6 ± 4.0
>25 kg/m²		125 (42.8%)
Smoking status at inclusion, *n* (%)	279	
Non-smoker ever		197 (70.6)
Former smoker		57 (20.4)
Smoker		25 (9.0)
At least one comorbidity prior to GCA diagnosis, *n* (%)	306	253 (82.7)
Comorbidities (≥2% of patients), *n* (%)	306	
Hypertension		140 (45.8)
Dyslipidemia		36 (11.8)
Diabetes mellitus		29 (9.5)
Cataract		19 (6.2)
Osteoporosis		18 (5.9)
Depression		17 (5.6)
Atrial fibrillation		16 (5.2)
Hypothyroidism		15 (4.9)
Hypercholesterolemia		12 (3.9)
Glaucoma		12 (3.9)
Breast cancer		10 (3.3)
Myocardial ischemia		9 (2.9)
Asthma		9 (2.9)
Sleep apnea syndrome		8 (2.6)
Osteoarthritis		8 (2.6)
Polymyalgia rheumatica		8 (2.6)
Cerebrovascular accident		7 (2.3)
Time between GCA diagnosis and inclusion (months), mean ± SD	306	21.0 ± 26.4
Concomitant treatments at GCA diagnosis, *n* (%)		
Antihypertensive agent	305	141 (46.2)
Antiplatelet agent	304	68 (22.4)
Proton pump inhibitor	305	67 (22.0)
Statin	305	40 (13.1)

GCA, giant cell arteritis; IQR, interquartile range; SD, standard deviation.

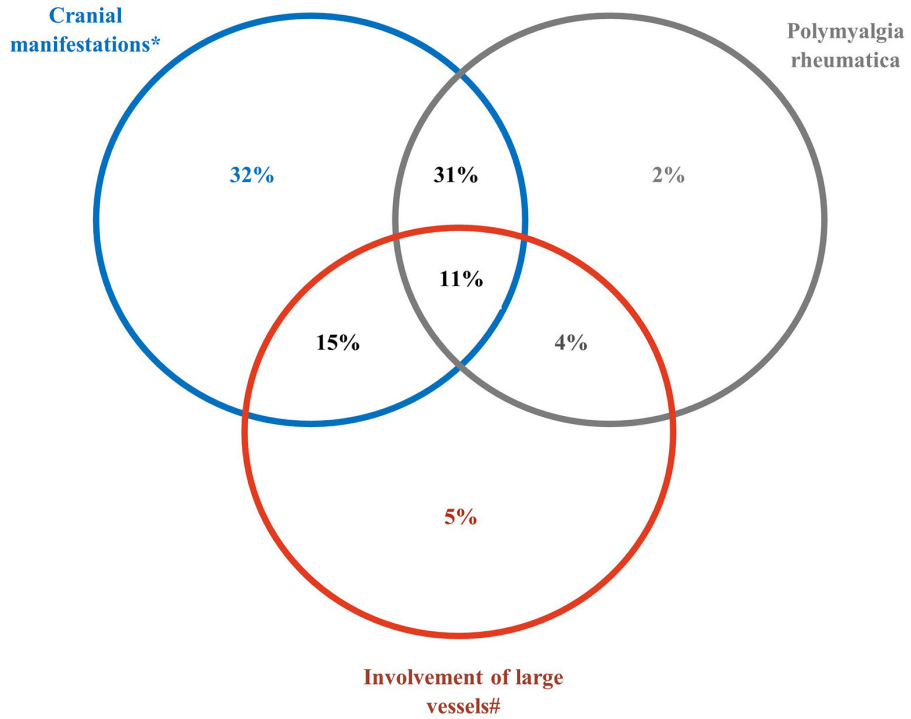

FIGURE 1 | Clinical phenotypes of giant cell arteritis at diagnosis. *The subset of cranial manifestations includes patients with strokes and transient ischemic attack(s). #The subset of large vessel involvement includes aortic aneurysm or dilatation, aortitis and/or involvement of aortic branch(s) in imaging, claudication of a limb, sign(s) of subclavian stenosis.

specialists, mainly general practitioners (56%), followed by ophthalmologists (10%), neurologists (7%), emergency physicians (6%), rheumatologists (5%), or internists (4%). Since the first GCA symptom, patients consulted a mean of 2.1 ± 1.2 specialists (general practitioners: 85%, ophthalmologists: 29%, neurologists: 12%, emergency doctors: 18%, internists: 19%, rheumatologists: 14%).

Initial Patient Presentation

At the study visit, the median time since GCA diagnosis was 13.0 months (IQR 5.0–26.0): 15.0 months (7.0–30.0) for patients with prevalent disease and 0.6 months (0.2–1.0) for those with a new diagnosis. Overall, 21% of patients had an early diagnosis, 57% a diagnosis within the standard timeframe, and 22% a late diagnosis.

In total, 271 (89%) patients had cranial involvement; 29 (9.5%) had an anterior ischemic optic neuropathy, 29 (9.5%) diplopia, and 5 (1.6%) blindness. Cranial involvement was associated with PMR in 42% of patients and with LV involvement in 26%. Isolated PMR and PMR associated with LV-GCA were diagnosed in 6% of patients. In all, 5% of patients had LV-GCA (i.e., LV involvement only) (**Figure 1**). The GCA characteristics at diagnosis are detailed in **Table 2**.

Cranial manifestations at diagnosis were more frequent in patients with early and standard-timeframe diagnoses (92% for both timeframes *vs.* 82% with late diagnosis). By contrast, patients with a late diagnosis more frequently had PMR symptoms (65 *vs.* 43–47%) and extracranial manifestations (49 *vs.* 27–31%).

Among patients with prevalent disease, those with at least one relapse initially experienced extracranial event(s) (excluding PMR) more often than those without any relapse since diagnosis (46 *vs.* 30%, $p = 0.009$). At the study visit, GCA activity assessed on a 100-mm VAS was higher for patients with incident than prevalent disease [median 27 (IQR 6–63) vs. 18 (5–47)] but the difference did not reach statistical significance ($p = 0.125$). GCA activity rated by physicians was significantly lower for patients with prevalent disease than patient with incident disease [median 3 (IQR 0–12) and 10 (2–53), $p = 0.0015$], and also showed smaller numbers compared with patient ratings.

Diagnostic Methods

GCA diagnosis can be based on clinical symptoms and physical examination, acute phase reactants, TAB, and/or imaging (high-resolution color Doppler ultrasonography, MRI of the temporal arteries, angio-CT or ^{18}FDG-PET). The mean number of methods used for GCA diagnosis was 1.9 ± 1.1. The methods used for GCA diagnosis and their contribution to the diagnosis are presented in **Figure 2**. Overall, TAB was the most frequently used technique (85%). High-resolution temporal artery Doppler ultrasonography, ^{18}FDG-PET and aortic angio-CT were also frequently performed, in 31, 26 and 30% of patients, respectively, whereas MRI of the temporal arteries was used in 7% of patients. Overall, TAB confirmed the diagnosis for 54.5% of patients,

TABLE 2 | Initial presentation of giant cell arteritis.

Variable at diagnosis	Incident disease* *N = 39 (%)*	Prevalent disease*			All patients *N = 306 (%)*
		No relapse N = 145 (%)	*≥1 relapse N = 122 (%)*	*Total N = 267 (%)*	
Cranial manifestations, *n* (%)	**33/39 (84.6)**	**132/145 (91.0)**	**106/122 (86.9)**	**238/267 (89.1)**	**271/306 (88.6)**
Headaches	30 (90.9)	110 (83.3)	84 (88.7)	204 (85.7)	234 (86.3)
Scalp sensitivity	18 (54.5)	55 (41.7)	62 (58.5)	117 (49.2)	135 (49.8)
Anomalies of the temporal arteries	13 (39.4)	68 (51.5)	50 (47.2)	118 (49.6)	131 (48.3)
Anterior ischemic optic neuropathy	2 (5.1)	21 (14.5)	6 (4.9)	27 (10.1)	*29 (9.5)*
Diplopia	5 (12.8)	12 (8.3)	12 (9.8)	24 (9.0)	*29 (9.5)*
Mouth pain or jaw claudication during mastication	18 (54.5)	65 (49.2)	49 (46.2)	114 (47.9)	132 (48.7)
Stroke or transient ischemic attack	1 (3.0)	12 (9.1)	3 (2.8)	15 (6.3)	16 (5.9)
Neck pain	1 (3.0)	3 (2.3)	2 (1.9)	5 (2.1)	6 (2.2)
Other	3 (9.1)	4 (3.0)	3 (2.8)	7 (2.9)	10 (3.7)
PMR symptoms, *n* (%)	**24/39 (61.5)**	**66/145 (45.5)**	**58/122 (47.5)**	**124/267 (46.4)**	**148/306 (48.4)**
Morning stiffness and/or pain in the shoulder girdle	21 (87.5)	53 (80.3)	52 (89.7)	105 (84.7)	126 (85.1)
Morning stiffness and/or pains in the pelvic girdle	11 (45.8)	34 (51.5)	37 (63.8)	71 (57.3)	82 (55.4)
Inflammatory arthromyalgia	12 (50.0)	38 (57.6)	42 (72.4)	80 (64.5)	92 (62.2)
Peripheral arthritis	4 (16.7)	9 (13.6)	7 (12.1)	16 (12.9)	20 (13.5)
Arthralgia	0 (0.0)	4 (6.1)	0	4 (3.2)	4 (2.7)
Other	2 (8.3)	5 (7.6)	2 (3.4)	7 (5.6)	9 (6.1)
Extracranial events (excluding PMR), *n* (%)	**8/39 (20.5)**	**44/145 (30.3)**	**56/122 (45.9)**	**100/267 (37.5)**	**108/306 (35.3)**
Thoracic or abdominal aortic aneurysm and/or dilatation	1 (12.5)	8 (18.2)	5 (8.9)	13 (13.0)	14 (13.0
Aortitis and-or involvement of aortic branch(s) in imaging	6 (75.0)	36 (81.8)	30 (53.6)	66 (66.0)	72 (66.7)
Angina and-or myocardial infraction	0 (0.0)	0	3 (5.4)	3 (3.0)	3 (2.8)
Claudication of an upper and/or lower limb	2 (25.0)	8 (18.2)	9 (16.1)	17 (17.0)	19 (17.6)
Sign(s) of subclavian stenosis	1 (12.5)	6 (13.6)	6 (10.7)	12 (12.0)	13 (12.0)
Other	0 (0.0)	5 (11.4)	11 (19.6)	16 (16.0)	16 (14.8)
ESR (mm/1st h) >50 mm/h, *n* (%)	**19/26 (73.1)**	**58/80 (72.5)**	**52/62 (83.9)**	**110/142 (77.5)**	**129/168 (76.8)**
CRP (mg/L) >25 mg/L, *n* (%)	**27/36 (75.0)**	**118/139 (84.9)**	**98/113 (86.7)**	**216/252 (85.7)**	**243/288 (84.4)**
General signs, *n* (%)	**25/39 (64.1)**	**111/145 (76.6)**	**91/122 (74.6)**	**202/267 (75.7)**	**227/306 (74.2)**
Fever >38°C	11 (44.0)	44 (39.6)	45 (50.0)	89 (44.3)	100 (44.2)
Weight loss	14 (56.0)	64 (57.7)	51 (46.0)	115 (56.9)	129 (56.8)
Alteration of the general condition	24 (96.0)	94 (84.7)	79 (86.8)	173 (85.6)	197 (86.8)

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PMR, polymyalgia rheumatica.

**Incident patients: diagnosis-to-visit interval <6 weeks; prevalent patients: diagnosis-to-visit interval ≥6 weeks. Bold values indicate proportion of patients in each group with available data.*

high-resolution temporal artery Doppler for 15.6%, ^{18}FDG-PET for 17%, aortic angio-CT for 8.8% and MRI for 3%. When performed, ^{18}FDG-PET most often established the diagnosis of GCA, in 70% of patients vs. 67% for TAB. In addition, ^{18}FDG-PET was more often used than TAB for patients with LV involvement (73 *vs.* 67%) (**Supplementary Table 1**). The use of vascular imaging was more frequent in patients with a late than early diagnosis (>3 *vs.* < 1 month): high-resolution temporal artery Doppler ultrasonography: 42 *vs.* 26% of patients; ^{18}FDG-PET: 46 *vs.* 17%; angio-CT: 35 *vs.* 19%.

Relapses and Complications

Patients with prevalent disease had experienced at least one relapse after diagnosis (46%), and most had one or two relapses (57 and 26%, respectively). The median time to first relapse was 10 months (IQR 5–19). Relapses were mainly evaluated according to clinical criteria (81%) and/or laboratory criteria of elevated levels of acute phase reactants (81%); they were rarely evaluated according to only laboratory criteria (14%). Cranial and rheumatic symptoms were the most frequent clinical criteria reported (in 52 and 44% of patients, respectively).

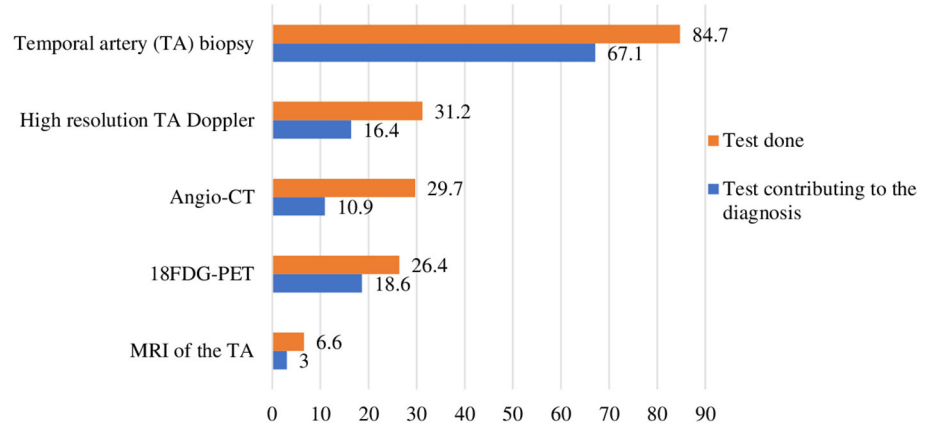

FIGURE 2 | Diagnostic tests for giant cell arteritis. Proportion of patients (%). CT, computed tomography; MRI, magnetic resonance imaging; ^{18}FDG-PET, ^{18}F-fluorodesoxyglucose positron emission tomography.

According to investigators' judgement, 16% of patients had at least one GCA complication since diagnosis, which was mainly ophthalmic (5%), psychiatric (3%) and or vascular (3%).

Treatment of GCA

All patients received GCs at least once after diagnosis, and GC therapy was ongoing in 89% at the study visit (**Table 3**). At diagnosis, intravenous pulse GCs were given to 54 (16%) patients for a median of 3 days (IQR 3–3). The median dose of GCs was higher for patients with incident than prevalent disease [40 (IQR 30–50) *vs.* 8 (5–15) mg/day]. Overall, the median cumulative oral GC dose, assessed in 87 patients, was 4,305 mg (IQR 1,920–7,000); the median cumulative oral GC dose, assessed in the 74 patients with prevalent disease, was 4,985 mg (IQR 2,838–7,170). For the 21 patients with relapse and with available data, the median cumulative dose was 7,400 mg (IQR 4,867–9,435). Most relapses (80%) were diagnosed in patients with ongoing GC therapy [median dose 10 mg/day (IQR 5–17)]; 11 and 3% of relapses occurred under ongoing immunosuppressive therapy or therapy with targeted biologics, respectively. Relapses were treated with GCs at a median prednisone equivalent dose of 20 mg/day (IQR 10–30) in 95% of cases, immunosuppressants in 21% and/or targeted biologics in 19%.

In addition, 29% of patients were receiving or received at least one adjunct treatment for GCA [immunosuppressants (19%) and/or targeted biologic agents (16%)], and 6% two different adjunct medications (**Table 4**). MTX and TCZ were the most frequently prescribed adjunct medications (19 and 15% of patients, respectively). For the 25 (8%) patients who stopped MTX before the study visit, the mean treatment duration was 16.8 ± 15.7 months. The current mean dose of MTX was 14.4 ± 4.8 mg/week for the 35 (11%) patients who were receiving the drug at inclusion. For the 9 (3%) patients who stopped TCZ before the study visit, the mean treatment duration was 21.9 ± 16.6 months. Other adjunct medications, namely azathioprine, cyclophosphamide, leflunomide, infliximab or adalimumab, were rarely prescribed (**Table 4**).

Overall, 37% of patients experienced at least one comorbidity related to or aggravated by the GCs use, mainly diabetes (12%), hypertension (10%), osteopenia/osteoporosis/osteoporotic fractures (7%), insomnia (3%), and infections (3%). Cataract and glaucoma were reported as GC-related events in 1% of patients for both events (**Supplementary Table 2**). Osteoporosis treatment and calcium-vitamin D were given to 47 and 37% patients, respectively, in the period following diagnosis of GCA and 61% received antiplatelet agents.

DISCUSSION

In the context of the rapidly evolving landscape of recommendations for managing GCA, this French study provides insights into current medical practices in hospital centers for GCA (GCA subtypes, patient pathway, diagnostic methods, and GCA treatments).

Overall, 306 patients under treatment for GCA were enrolled by 69 hospital-based specialists from 53 centers in 2018. Most patients were females and most were at least 70 years old at the study visit, in accordance with the well-known characteristics of GCA (12–15). General practitioners referred half of the patients to the specialists who participated in the study.

At initial presentation, cranial manifestations (isolated or not) were predominant (89% of patients), as expected and previously reported (14). Isolated LV-GCA was diagnosed in only 5% of patients. Delayed diagnosis was still common (>3 months after the first medical event in 22% of patients), in particular for patients with PMR symptoms or extracranial events.

Probably in line with the common cranial manifestations of GCA and headache, TAB remained the most commonly performed diagnostic test for GCA and was used in 85% of patients. This proportion was consistent with the proportion from a French retrospective study (91%) conducted in two hospital centers (13) but much higher than that reported in a study (51%) based on national administrative health insurance claims data between 2007 and 2015 (12). This difference may

TABLE 3 | Glucocorticoids for giant cell arteritis since diagnosis.

Glucocorticoids (GCs)	Number of analyzed patients	Incident disease* (*N = 39*)	Prevalent disease*		All patients (*N = 306*)
			No relapse (N = 145)	*≥1 relapse (N = 122)*	*Total (N = 267)*
Number of GC courses, *n* (%)	306				
1		39 (100.0)	142 (97.9)	94 (77.0)	236 (88.4)	275 (89.9)
2		0 (0.0)	3 (2.1)	26 (21.3)	29 (10.9)	29 (9.5)
3		0 (0.0)	0 (0.0)	2 (1.6)	2 (0.7)	2 (0.7)
GC course duration (months), median (IQR)	306	1.00 (0.00–1.00)	10.00 (4.00–16.00)	20.00 (11.50–32.50)	14.00 (7.00–25.00)	12.50 (5.00–23.00)
Ongoing treatment with GCs at study visit (mg), *n* (%)	306	39 (100.0)	131 (90.3)	103 (84.4)	234 (87.6)	273 (89.2)
Current dose of GCs at study visit (mg), median (IQR)	273	40.00 (30.00–50.00)	9.00 (5.00–15.00)	8.00 (5.00–12.00)	9.00 (5.00–15.00)	9.00 (5.00–20.00)
Total cumulative oral dose of GCs (mg), median (IQR)	87	1080.00 (660.00–1800.00)	4350.00 (2580.00–5670.00)	7400.00 (4867.00–9435.00)	4985.00 (2838.00–7170.00)	4305 (1920–7000)

IQR, interquartile range.

**Incident disease: diagnosis-to-visit interval <6 weeks; prevalent disease: diagnosis-to-visit interval ≥6 weeks.*

TABLE 4 | Adjunctive treatments for giant cell arteritis since diagnosis.

Variable	Number of analyzed patients	Total *N = 306*
At least one adjunct treatment, *n* (%)	**306**	**90 (29.4)**
Immunosuppressants, *n* (%)	306	59 (19.3)
Methotrexate		58 (18.9)
Azathioprine		2 (0.7)
Cyclophosphamide		1 (0.3)
Leflunomide		1 (0.3)
Targeted biologic agents, *n* (%)	306	48 (15.7)
Adalimumab		1 (0.3)
Infliximab		1 (0.3)
Tocilizumab		47 (15.4)

be explained by the fact that the ARTEMIS study did not enroll patients exclusively seen by community physicians (office-based rheumatologists or general practitioners who could have practices different from hospital-based specialists). Also, vascular imaging modalities were frequently used (from 26 to 31% of patients depending on the imaging performed) and contributed to the diagnosis, in particular for patients with extracranial manifestations. This observation may reflect a shift toward imaging techniques for GCA diagnosis, in accordance with recent European recommendations (7, 8). However, the use of large-vessel imaging was not systematic, which could explain the small proportion (11%) of patients with a diagnosis of non-cranial GCA.

Our study showed a high proportion of patients with GCA relapse(s) since diagnosis (46%), with a median time to first relapse of 10 months. These results are consistent with previous findings from a French monocentric study showing 52% relapse after a median of 12 months after diagnosis (15) and with the proportion of relapsing patients (42%) in a meta-analysis of non-interventional studies (16). In addition, we observed a significantly higher proportion of relapsing patients who presented extra-cranial event(s) at GCA diagnosis as compared with patients with no relapse during follow-up. In a retrospective monocentric French study, LV-GCA was found as an independent factor of relapse (hazard ratio 1.49, 95% confidence interval 1.002–2.12; $p = 0.04$) (15).

The toxicity related to GCs depends on both the daily dose and cumulative dose (14, 17). In our study, the high median GC dose of patients with incident disease (40 mg/day) was consistent with the median starting dose of GCs analyzed from a US database (50 mg/day) as well as the cumulative GC dose (4,305 and 4,800 mg, respectively) (14). This GC dose of patients with incident disease in our study is somewhat lower than the mean initial dose prescribed in a French population-based study (mean 41.7 *vs.* 54.5 mg/day) (18). As compared with non-hospital physicians, hospital specialists may prescribe lower prednisone doses in non-complicated GCA, the most frequent form of the disease.

Overall, after a median GCA duration of 13 months (15 months for prevalent patients), 37% of patients experienced at least one comorbidity related to or

aggravated by the GCs taken (mainly diabetes, hypertension, osteopenia/osteoporosis/osteoporotic fractures, insomnia, and infections). The lower occurrence of side effects linked to the use of GCs in our study compared to the much higher previously reported figures (9), may be related to a lower cumulative dose and a better management of corticosteroids tolerance during the last decades but is still an issue in these older patients.

Overall, 29% of the studied patients received at least one adjunct agent since GCA diagnosis. MTX and TCZ were the most-prescribed GC-sparing agents (19 and 15% of patients, respectively). The doses of MTX used (mean 14.4 ± 4.8 mg/week) were in agreement with or close to recommendations, the minimum recommended dose being 15 mg/week for EULAR and from 7.5 to 15 mg/week for French recommendations (6, 7). By comparison, regarding the proportions of patients receiving an adjunct treatment, the French study based on national administrative health insurance claims data showed a slightly lower proportion of patients receiving MTX between 2007 and 2015 (12%) and no patients receiving TCZ during this period (12). The new prescriptions of TCZ observed in 2018 should be seen in relation to the recent approval of TCZ in this indication (in 2017).

Our real-world data are based on a large sample of patients with GCA defined as per physician judgement and without imposed classification criteria. Thus, the study provides findings for GCA management based on usual medical practices. The limitations of our study are inherent to its non-interventional design and that studied variables were analyzed only when available in patients' medical files. In addition, only GCA patients under treatment at the study visit had to be included, which may have led to an increased proportion of patients with long-standing therapies. Finally, because the study did not enroll GCA patients exclusively seen by community physicians, the extrapolation of our findings to other populations is cautioned.

In conclusion, this large observational study conducted in patients with recently diagnosed GCA provides insight into current medical practices for GCA in France. Our data show that non-cranial GCA remains a rare clinical phenotype of the disease despite the increasing use of LV imaging. In addition, the substantial proportion of patients with relapsing disease was confirmed, with high cumulative GC doses and adjunct medications (mainly MTX and TCZ) in one third of patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee (authorization No: 2018-A00841-54. 2-18-37)_Agence régionale de Santé Toulouse/France. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

AM, EH, II, MP, and VD-P contributed to conception, design, and analyses interpretation of the study. AM organized the database. AM and II wrote the first draft of the manuscript. EH, HB, LS, and VD-P wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2021.732934/full#supplementary-material

REFERENCES

1. Zöller B, Li X, Sundquist J, Sundquist K. Occupational and socioeconomic risk factors for giant cell arteritis: a nationwide study based on hospitalizations in Sweden. *Scand J Rheumatol.* (2013) 42:487–97. doi: 10.3109/03009742.2013.793777
2. Gonzalez-Gay MA, Vazquez-Rodriguez TR, Lopez-Diaz MJ, Mirand-Filloy JA, Gonzalez-Juanatey C, Martin J, et al. Epidemiology of giant cell arteritis and polymyalgia rheumatica. *Arthritis Rheum.* (2009) 61:1454–61. doi: 10.1002/art.24459
3. Koster MJ, Mtteson EL, Warrington KJ. Large-vessel giant cell arteritis: diagnosis, monitoring and management. *Rheumatology.* (2018) 57(suppl_2):ii32-ii42. doi: 10.1093/rheumatology/kex424
4. Ness T, Bley TA, Schmidt WA, Lamprecht P. The diagnosis and treatment of giant cell arteritis. *Dtsch Arztebl Int.* (2013) 110:376–86. doi: 10.3238/arztebl.2013.0376
5. Bienvenu B, Lambert M, Agard C, André M, Benhamou Y, Bonnotte B, et al. Management of giant cell arteritis: recommendations of the French study group for large vessel vasculitis (GEFA). *Rev Med Interne.* (2016) 37:154–65. doi: 10.1016/j.revmed.2015.12.015
6. Protocole National de Diagnostic et de Soins (PNDS). *Artérite à Cellules Géantes (Horton).* (2017). Révision (2020). Available online at: https://

www.has-sante.fr/upload/docs/application/pdf/2017-08/pnds_-_arterite_a_cellules_geantes.pdf (accessed June 25, 2020).
7. Dejaco C, Ramiro S, Duftner C, Besson FL, Bley TA, Blockmans D, et al. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. *Ann Rheum Dis.* (2018) 77:636–43 doi: 10.1136/annrheumdis-2017-212649
8. Hellmich B, Agueda A, Monti S, Buttgereit F, de Boysson H, Brouwer E, et al. (2018). Update of the EULAR recommendations for the management of large vessel vasculitis. *Ann Rheum Dis*. (2020) 79:19–30. doi: 10.1136/annrheumdis-2019-215672
9. Proven A, Gabriel SE, Orces C, O'Fallon WM, Hunder GG. Glucocorticoid therapy in giant cell arteritis: duration and adverse outcomes. *Arthritis Rheum.* (2003) 49:703–8. doi: 10.1002/art.11388
10. 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) 377:317–28. doi: 10.1056/NEJMoa1613849
11. Stone JH, Bao M, Han J, Aringer M, Blockmans D, Brouwer E, et al. Long-term outcome of tocilizumab of patients with giant cell arteritis. Results from part 2 of the GIACTA trial. *Ann Rheum Dis*. (2019) 78:145–6. doi: 10.1136/annrheumdis-2019-eular.2099
12. Mahr A, Belhassen M, Paccalin M, Devauchelle-Pensec V, Nolin M, Gandon S, et al. Characteristics and management of giant cell arteritis in France: a study based on national health insurance claims data. *Rheumatology*. (2020) 59:120–8. doi: 10.1093/rheumatology/kez251
13. De Boysson H, Liozon E, Ly KH, Dumont A, Delmas C, Aouba A. The different clinical patterns of giant cell arteritis. *Clin Exp Rheumatol.* (2019) 117:57–60.
14. Gale S, Wilson JC, Chia J, Trinh H, Tudkwell K, Collinson N, et al. Risk associated with cumulative oral glucocorticoid use in patients with giant cell arteritis in real-world databases from the USA and UK. *Rheumatol Ther*. (2018) 5:327–40. doi: 10.1007/s40744-018-0112-8
15. Dumont A, Parienti JJ, Delmas C, Boutemy J, Maigné G, Silva MM, et al. Factors associated with relapse and dependence on glucocorticoids in giant cell arteritis. *J Rheumatol.* (2020) 47:108–16. doi: 10.3899/jrheum.181127
16. Mainbourg S, Addario A, Samson M, Puéchal X, François M, Durupt S, et al. Prevalence of giant cell arteritis relapse in patients treated with glucocorticoids: a meta-analysis. *Arthritis care & research.* (2019) 72:838–49. doi: 10.1002/acr.23901
17. Buttgereit F, Matteson EL, Dejaco C, Dasgupta B. Prevention of glucocorticoid morbidity in giant cell arteritis. *Rheumatology*. (2018) 57(suppl_2):ii11-ii21. doi: 10.1093/rheumatology/kex459
18. Pugnet G, Sailler L, Bourrel R, Montastruc JL, Lapeyre-Mestre M. Is statin exposure associated with occurrence or better outcome in giant cell arteritis? results from a French population-based study. *J Rheumatol.* (2015) 42:316–22. doi: 10.3899/jrheum.140906

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EDITED BY
Andreas P. Diamantopoulos,
Akershus University Hospital, Norway

REVIEWED BY
Catherine Hill,
University of Adelaide, Australia
Mohammad Bardi,
University of British Columbia, Canada

*CORRESPONDENCE
Jelka Kramarič
jelka.kramaric@gmail.com

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Performance of leflunomide as a steroid-sparing agent in giant cell arteritis: A single-center, open-label study

Jelka Kramarič[1,2]*, Žiga Rotar[1,2], Matija Tomšič[1,2] and Alojzija Hočevar[1,2]

[1]Department of Rheumatology, University Medical Centre Ljubljana, Ljubljana, Slovenia, [2]Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

Background: The management of giant cell arteritis (GCA) remains challenging and many patients require prolonged glucocorticoid treatment due to high disease relapse rates. We aimed to evaluate the role of leflunomide as a steroid-sparing agent in GCA.

Methods: This prospective open-label study included patients diagnosed with GCA between July 2014 and August 2020 and followed them for 96 weeks. At the time of diagnosis all patients received treatment following a predefined glucocorticoid regimen. At week 12 of follow-up, 10 mg of leflunomide per day was recommended as an adjunctive therapy. The decision to start with leflunomide treatment was patient-dependent. Follow-up visits were performed adhering to a predetermined protocol. The number of relapses, the cumulative glucocorticoid dose and treatment-related adverse events were recorded and compared between glucocorticoid-only and leflunomide groups.

Results: Of the 215 GCA patients [67.6% female, median (IQR) age 74 (66–79) years], 151 (70.2%) received leflunomide at week 12 (leflunomide group); the others continued with glucocorticoids (glucocorticoid-only group). During the study 64/215 (29.8%) patients relapsed. Of the 51 patients who relapsed after 12 weeks, 22/151 patients (14.6%) and 29/64 patients (45.3%) were in the leflunomide and glucocorticoid-only group, respectively ($p = 0.001$; NNT 3.3 for leflunomide). Furthermore, 80/151 patients in the leflunomide group managed to stop glucocorticoids at week 48 [with relapses in 6/80 patients (7.5%)]. The cumulative glucocorticoid dose was lower in the leflunomide group ($p = 0.009$).

Conclusion: In our cohort, leflunomide safely and effectively reduced the GCA relapse rate and demonstrated a steroid-sparing effect in over three quarters of patients.

KEYWORDS

giant cell arteritis, open-label study, leflunomide, relapses, steroid sparing

Introduction

Giant cell arteritis (GCA) represents the most common primary vasculitis of large and medium-sized arteries in the population aged over 50 in Europe and North America (1). It is a rheumatologic emergency and as such requires prompt anti-inflammatory treatment to prevent irreversible ischemic complications (2–4). Glucocorticoids remain the cornerstone of treatment due to their rapid onset of action (5). Unfortunately, almost half of patients relapse during glucocorticoid tapering, and around half after glucocorticoid withdrawal (4, 6). Therefore, many patients need prolonged treatment resulting in high cumulative glucocorticoid doses (5). Therefore, patients are at risk of developing glucocorticoid-related adverse events and complications such as diabetes, arterial hypertension infections, osteoporosis, fractures and steroid myopathy (7). Many conventional synthetic and biologic disease-modifying anti-rheumatic drugs (csDMARDs, bDMARDs) have been studied for their steroid-sparing effect in treating GCA. A superior efficacy compared to glucocorticoids, as well as reduced cumulative glucocorticoid exposure and increased rate of sustained remission was compellingly shown only for tocilizumab (8). However, bDMARDs are contraindicated in some patients and are associated with a significant cost. Among csDMARDs, methotrexate is recommended as an alternative, despite the very modest evidence supporting its use (9, 10). Nevertheless, the use of methotrexate is contraindicated in chronic kidney disease, which is relatively common in the elderly population, which is the population most often affected by GCA.

Leflunomide is a safe and effective csDMARD for the treatment of inflammatory arthritides as well as systemic vasculitides (e.g., granulomatosis with polyangiitis and Takayasu arteritis) (11, 12). Due to its mechanism of action the potential effectiveness of leflunomide is expected in GCA, as it suppresses the production of proinflammatory cytokines through the activation of dendritic cells and also weakens the action of the T-cell response (13, 14).

There are no randomized controlled clinical trials supporting the efficacy of leflunomide as a steroid-sparing agent in GCA, but data from a few single-center studies, case series and case reports are promising (15–21). Our center reported in 2019 a study on leflunomide in GCA patients, comparing 30 patients treated with leflunomide vs. 46 on glucocorticoids (15). In the current extended study (both in the number of patients and the study period) we evaluated the effectiveness of leflunomide in the largest cohort of patients with GCA reported up-to-date.

Methods

Setting

This prospective open-label study was performed at the Department of Rheumatology, University Medical Center Ljubljana, a secondary/tertiary level teaching hospital, where we manage most GCA cases from the region using our fast-track protocol (4).

Patients

In the present study we enrolled patients diagnosed with GCA between July 2014 and August 2020.

GCA diagnosis was based on the corresponding clinical and laboratory features and either the positive result of a temporal artery biopsy as defined by the 1990 American College of Rheumatology criteria for the classification of GCA (22) and/or the positive result of imaging [color Doppler sonography of seven arterial territories–paired temporal, facial, occipital, carotid, vertebral, subclavian and axillary, or positron emission tomography/computed tomography (PET/CT) with the use of 18F-fluoro-2-deoxy-D-glucose (18F-FDG)].

Baseline evaluation and follow-up

The baseline patient work-up included a thorough history of GCA symptoms, comorbidities, a complete physical examination, extensive laboratory tests and imaging (color Doppler sonography or 18F-FDG PET/CT) or a temporal artery biopsy.

Follow-up visits with predetermined clinical evaluation and laboratory tests were performed at 4, 12, 24, 48, 52 (± 2) and 96 (± 2) weeks after diagnosis. Additional unscheduled visits were arranged for patients who relapsed during glucocorticoid tapering or after glucocorticoid discontinuation.

Patients who completed all scheduled follow-up visits were included in the analysis.

Disease relapse was defined as the disease worsening or new disease activity after the initial remission. We subdivided the observed relapses into laboratory-only, clinical-only or clinical and laboratory. Other reasons for the observed symptoms and/or elevated inflammatory markers (i.e., infections, malignancy, other underlying disease) had to be excluded.

Clinical relapse was defined as the reappearance of signs of cranial ischemia (headache, yaw claudication, visual disturbances–usually objectivized by an ophthalmologist), constitutional symptoms (fever, weight loss, night

sweating), symptoms of polymyalgia rheumatica, and in the case of limb ischemia, the worsening of the ischemia after initial improvement after treatment. The symptoms/signs have to improve after the intensification of immunomodulatory treatment.

In the laboratory we monitored the C-reactive protein and erythrocyte sedimentation rate. A persistent increase of C-reactive protein and erythrocyte sedimentation rate, after the exclusion of infection and other causes for elevation of inflammatory parameters (e.g., malignancy), that responded to the escalation of immunomodulatory treatment was documented as a laboratory GCA relapse.

We recorded the number of relapses during the first 96 weeks of treatment, the cumulative glucocorticoid dose for each patient at 96 weeks, and adverse events associated with glucocorticoids or leflunomide.

Treatment protocol and patient stratification

The detailed study protocol has been already described (15). Briefly, according to EULAR recommendations, we initiated treatment with glucocorticoids in all patients at the time of GCA diagnosis (23, 24). The initial dose of oral methylprednisolone was 0.8 mg/kg of body weight once per day (qd), but no <32 mg qd and no more than 48 mg qd. Patients with cranial GCA experiencing ischemic complications such as visual disturbance and those with extracranial large vessel GCA additionally received methylprednisolone 250 mg intravenously for three consecutive days prior to receiving methylprednisolone orally.

The tapering of glucocorticoid therapy started after 2–4 weeks. The dose of methylprednisolone was reduced by 4 mg weekly to 16 mg qd, then 2 mg each other week to 8 mg qd, then 1 mg monthly to a maintenance dose of 4 mg qd. At week 48 we discontinued glucocorticoid treatment in patients in the leflunomide group who were in remission during the first 48 weeks of follow-up. Patients who chose to remain in the glucocorticoid-only group and patients in the leflunomide group with a relapse continued treatment with the lowest effective glucocorticoid dose after week 48.

At week 12 the add-on therapy with leflunomide 10 mg qd was offered to all patients without contraindications for leflunomide (e.g., liver failure, bone marrow suppression). Patients who refused treatment with leflunomide were allocated to the glucocorticoid-only group.

In cases of GCA relapse, the methylprednisolone dose was temporarily increased by 8–12 mg qd on top of the last previously effective dose and leflunomide (10 mg qd) was added to the treatment for patients in the glucocorticoid-only group. In cases of GCA relapse in patients who were in the leflunomide group, the methylprednisolone dose was increased as described above, and the dose of leflunomide was increased from 10 to 20 mg qd. In cases of active GCA, despite this intervention or in cases of adverse events attributable to leflunomide, leflunomide was substituted with oral methotrexate (15 to 20 mg weekly) or a bDMARD (tocilizumab or ustekinumab).

Adverse events

Adverse events were systematically recorded with particular focus on 17 types of adverse events attributable to either glucocorticoids or leflunomide: steroid diabetes, steroid myopathy, osteoporotic fracture, cataract, glaucoma, severe infection (defined as a need for antibiotic treatment or hospital admission, including tuberculosis), hair loss, weight loss, diarrhea, significant increase in blood pressure (defined as the need to increase or institute antihypertensive therapy), elevated transaminases, skin bruises, skin rash, leflunomide induced pneumonitis, polyneuropathy and bone marrow toxicity.

Ethical standards

The study was approved by the National Medical Ethics Committee, approval number 112/09/14.

All patients provided their written consent for the use of their demographic and clinical data.

Statistical analysis

Descriptive statistics were used to analyse the studied population. The results were expressed as medians and interquartile ranges (IQR) for metric continuous variables with skewed distribution, and as numbers and proportions for categorical variables. To test the differences between the observed groups, we used the Mann–Whitney U test for metric and Fisher's exact test for categorical variables. The significance threshold selected in all analyses was set at 0.05. The Jamovi (Sydney, Australia) software (version 2.3.0) was used for statistical calculations.

Results

Stratification of GCA patients and baseline patient characteristics

During the 74-month period, we identified 266 patients with newly diagnosed GCA, of whom 51 patients did not complete all the scheduled visits and were therefore excluded from further analyses. Of the remaining 215 patients, 151 (70.2%) chose to start leflunomide (i.e., leflunomide group) and 64 (29.8%) chose not to (i.e., glucocorticoid-only group) (Figure 1).

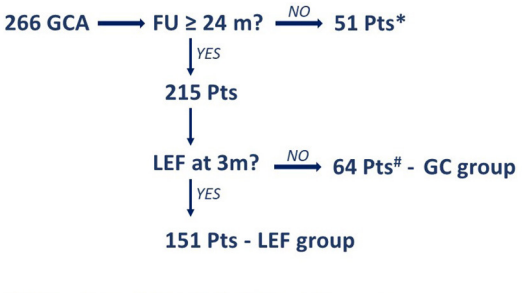

FIGURE 1
Flow chart in giant cell arteritis patients.

All patients underwent a vascular ultrasound, and 168/215 (78.1%) had a positive temporal artery ultrasound. In addition, 42 of 47 patients with a negative temporal artery ultrasound had ultrasound findings consistent with vasculitis in one of the other examined arteries. A temporal artery biopsy was performed in 100 patients, and was positive in 86 cases (86.0%). A PET/CT was performed in 27 patients and was consistent with vasculitis in 24 cases (88.9%).

The baseline demographic and clinical characteristics as well as inflammatory markers of the 215 GCA patients (67.6% female) who were followed for at least 96 weeks are presented in Table 1, column A. Their median (IQR) age was 74 (66–79) years. Cranial GCA was diagnosed in 138 (64.2%) patients and the rest had extracranial large vessel GCA. There were no significant differences in baseline demographic and clinical characteristics or inflammatory markers between the leflunomide and glucocorticoid-only group (Table 1, column B).

Follow-up from week 0 to week 96

During the study 64/215 (29.8%) patients relapsed. Overall, we documented 81 relapse episodes, as some patients had more than one relapse: we documented one relapse in 51 (79.7%) patients, two relapses in 10 (15.6%) patients, three relapses in two (3.1%) patients and four relapses in one (1.6%) patient).

Patients with extracranial large vessel GCA relapsed more frequently compared to cranial limited GCA (46.9% patients had large vessel involvement in the relapsing GCA group, compared to 31.1% cases of large vessel involvement in the non-relapsing GCA group, $p = 0.031$).

In 18 patients the first relapse occurred during the first 12 weeks after diagnosis (i.e., before adding the leflunomide), while 63 episodes occurred in 51 patients from week 12 to week 96 of the follow-up.

Of the 51 patients with a relapse after week 12 of follow-up, 22 patients were in the leflunomide group [22/151 patients (14.6%); 25 episodes] and 29 in the glucocorticoid-only group [29/64 patients (45.3%); 38 episodes]. The difference in the relapse rates between the groups was significant ($p < 0.001$), with the number needed to treat (NNT) for leflunomide standing at 3.3 (95% CI 2.3; 5.5). Among the documented relapses, 59% were laboratory-only, 6% were clinical-only and 35% were concurrently clinical and laboratory.

In 18 relapsing patients leflunomide was increased from 10 to 20 mg. In 14 patients, methotrexate was prescribed after relapse. In two relapsing patients ustekinumab was used and in one patient tocilizumab was used after leflunomide failure (however this patient was finally treated with secukinumab).

Follow-up of leflunomide group after glucocorticoid withdrawal

In 80 (53.0%) of the 151 patients in the leflunomide group, glucocorticoid treatment was discontinued at week 48, as per protocol. Three patients decreased the methylprednisolone dose after 48 weeks from 4 mg qd to 2 mg qd. The rest continued treatment with methylprednisolone of 4 mg qd. During the follow-up period in the leflunomide group after glucocorticoid discontinuation (from week 48 to week 96) we documented relapse in 6 out of the 80 (7.5%) patients (these relapses were included in the quota of all relapses in leflunomide group).

Cumulative glucocorticoid dose at week 96

At the last follow-up visit (week 96) the cumulative median (IQR) prednisolone-equivalent doses were 7.0 (5.2; 7.7) g and 7.7 (7.0; 7.9) g in the leflunomide and glucocorticoid-only group, respectively. The difference in cumulative glucocorticoid dose was significant ($p = 0.009$).

Adverse events

We documented at least one of the adverse events of special interest in 187 (87.0%) patients. Adverse events were observed in 87.4 and 85.9% of patients in the leflunomide and glucocorticoid-only group, respectively. In total we observed 419 adverse events (Table 2, column A). The two adverse events that were significantly more frequent in the leflunomide group were hair loss ($p = 0.016$) and diarrhea ($p = 0.016$). None of the patients had leflunomide-associated bone marrow toxicity, pneumonitis or polyneuropathy. The frequencies of adverse events are shown in Table 2, column B.

Forty-one out of 151 (27.2%) patients discontinued leflunomide due to one or more adverse events, after a median (IQR) 18 (7, 27) weeks of treatment.

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TABLE 1 Baseline characteristics of giant cell arteritis patients in the leflunomide and glucocorticoid-only group.

Characteristics	A	B		
	ALL GCA ($n = 215$)	LEF ($n = 151$; 70%)	GC ($n = 64$; 30%)	p value
Female	146 (67.9%)	71.5	59.4	0.110
Age (years)	74 (66; 79)	73 (66; 78)	77 (69; 84)	0.177
Constitutional symptoms	161 (74.9%)	73.5	78.1	0.606
Polymyalgia rheumatica	31 (14.4%)	15.9	10.9	0.402
Headache	149 (69.3%)	71.5	64.1	0.332
Jaw claudication	95 (44.2%)	46.4	39.1	0.369
Visual symptoms	46 (21.4%)	19.9	25.0	0.467
Visual loss	13 (6.0%)	4.6	9.4	0.214
Stroke	4 (1.9%)	2.6	0	0.320
Large vessel vasculitis	77 (35.8%)	33.1	42.2	0.217
ESR (mm/h)	83 (60; 110)	80 (60; 110)	91 (60; 111)	0.610
CRP (mg/l)	91 (46; 140)	91 (47; 140)	95 (37; 137)	0.960

GCA, giant cell arteritis; LEF, leflunomide group; GC, glucocorticoid-only group; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein. Results are presented as n (%), except age, ESR, and CRP which are presented as median (IQR).

Discussion

The management of GCA remains a challenge, despite new insights into disease pathogenesis, improved diagnostic options, fast-track protocols and approval of bDMARDs for its treatment. In spite of the growing choice of treatment options, glucocorticoids have remained the mainstay of therapy for GCA regardless of their long-term adverse effects and increased awareness of the importance of glucocorticoid-sparing treatment regimens. Among csDMARDs, methotrexate has been extensively studied in GCA but without much success (9, 25). Leflunomide, which is an effective and safe csDMARD, has not been extensively studied in GCA, even though its mechanism of action supports its potential benefit in the treatment of GCA due to its immunomodulatory effect through the inhibition of dendritic cell maturation, which is considered the principal pathogenetic mechanism in GCA (13, 14). Leflunomide also modulates interleukin-6 levels, known to be elevated in GCA (26).

To our knowledge, we have reported the largest cohort of patients who have cranial or large vessel GCA, were treated with an add-on therapy with leflunomide and followed for 96 weeks. We focused on the occurrence of relapses, assessing the potential steroid-sparing effect of leflunomide and its safety.

After week 12 of follow-up, i.e., after the cohort was split into leflunomide and glucocorticoid-only group, we observed significantly fewer relapses in the leflunomide group, with an NNT for leflunomide of ∼3 patients. Furthermore, even after the glucocorticoids were discontinued at week 48 for more than half of the patients in the leflunomide group, only 7.5% of patients relapsed in the period from week 48 to week 96. This data demonstrates that most patients in whom glucocorticoid can be discontinued after 48 weeks remain in remission on leflunomide alone for at least a year. Additionally, these patients achieved and remained in remission with a significantly lower cumulative glucocorticoid dose at week 96. This effect was reached by adding a low-dose leflunomide of only 10 mg qd, which is lower than the standard dose for treatment of rheumatoid arthritis (27).

There were no serious or life-threatening adverse events observed that were attributable only to leflunomide, such as hypersensitivity reaction, bone marrow toxicity, pneumonitis or polyneuropathy. The rate of adverse events observed was similar between the two groups, since both groups received glucocorticoids. The two adverse events that were significantly more common in the leflunomide group were hair loss and diarrhea, which were resolved after discontinuation of leflunomide, suggesting that the risk of persistent and relapsing GCA and prolonged treatment with glucocorticoids outweighs the risk of leflunomide-associated toxicity. Moreover, there was no significant difference in the occurrence of severe infections between the groups, a finding further supporting the use of leflunomide. Numerically speaking, the infection rate was even lower in leflunomide group. We also found our results to be in line with a recent study in large vessel GCA, where a 24.3% discontinuation rate was reported (20). Similarly, in studies in rheumatoid arthritis, the drop-out due to leflunomide adverse events was 25% (28).

These data extend previous observations from the first ever prospective observational single-center study, conducted at our center, which confirmed a significant difference in the rate of relapses in the group receiving leflunomide in addition to

TABLE 2 Adverse events in the leflunomide and glucocorticoid-only group.

Adverse event	A	B		
	ALL GCA [$n = 215$; n (%)]	LEF ($n = 151$; %)	GC ($n = 64$; %)	p value
Bruises	119 (55.3%)	52.3	62.5	0.180
Steroid diabetes	61 (28.4%)	27.2	31.3	0.620
Steroid myopathy	49 (22.8%)	25.8	15.6	0.113
Osteoporotic fracture	10 (4.7%)	5.3	3.1	0.727
Cataracts	29 (13.5%)	11.9	17.2	0.382
Glaucoma	3 (1.4%)	0.7	3.1	0.212
Severe infection	43 (20.0%)	17.2	26.6	0.137
Hair loss	54 (25.1%)	29.8	14.1	0.016
Weight loss	14 (6.5%)	7.9	3.1	0.239
Diarrhea	19 (8.8%)	11.9	1.6	0.016
Increased BP	9 (4.2%)	4.6	3.1	1.0
Elevated transaminases	5 (2.3%)	2.6	1.6	1.0
Bone marrow toxicity	0	0	0	-
Leflunomide rash	1 (0.5%)	0.7	-	-
Tuberculosis	0	0	0	-
Leflunomide pneumonitis	0	0	-	-
Leflunomide neuropathy	0	0	-	-

GCA, giant cell arteritis; LEF, leflunomide group; GC, glucocorticoid-only group; BP, blood pressure.

standard glucocorticoid therapy compared to the control group receiving glucocorticoids alone during the first 48 weeks of follow-up (13.3 vs. 39.1%, $p = 0.02$), but with a lower number of enrolled patients (76 patients) (15).

A recent prospective Indian observational study reported 22 patients newly diagnosed with cranial-only GCA with an add-on therapy with leflunomide to a predefined glucocorticoid regimen at week 0, demonstrating that the maintenance of continuous steroid-free remission was achieved in 68% of patients for a median follow-up period of 24 months (18). Seven (31.8%) patients in this cohort experienced a clinical relapse after a median of 12 months after initial remission, a rate significantly higher than in our cohort; however, due to the different design of the study and limited number of patients, a comparison is inapplicable.

Another recent, though retrospective study from the UK reported long-term experience with the use of leflunomide in a cohort of 70 patients with large-vessel GCA (20). Of all the patients on leflunomide, 23% experienced at least one relapse; however, patients starting leflunomide due to a relapse later on in the course of the disease course were also included. Compared to our findings, we can speculate that the relapse rate might be lower if all patients were started on leflunomide early on in the course of the disease, even though our cohort included large-vessel as well as cranial GCA patients. The findings in this study were additionally supported by the use of imaging, confirming a positive response in the majority of patients.

To date, there are only a few other available pieces of data supporting the effectiveness of leflunomide as a steroid-sparing agent in GCA from a few other single-center studies, case series and case reports. A study carried out in Norway reported 11 retrospectively identified patients with difficult-to-treat GCA receiving leflunomide showing a significant reduction of CRP ($p = 0.02$) and a significantly smaller dose of prednisolone ($p = 0.02$) as early as after 3 months of treatment (17). Another retrospective Norwegian study, comparing leflunomide and methotrexate in the treatment of GCA, showed a significant difference in the time-to-remission rate in patients treated with leflunomide (56.4 vs. 86.4 weeks for leflunomide and methotrexate, respectively) (16). A case series from the UK demonstrated that 22 out of 23 patients (9 with difficult-to-treat GCA and 14 with difficult-to-treat polymyalgia rheumatica) had a complete or partial response to leflunomide, which was well-tolerated in all except in three patients, who experienced rashes, diarrhea and peritoneal abscesses (21).

Most of the up-to-date published studies are retrospective in nature and dealt with patients with difficult-to-treat diseases, some of whom had previously been unsuccessfully treated with another csDMARD (e.g., methotrexate), and who mostly

required higher doses of glucocorticoids than the standard tapering regimen. It is therefore difficult to establish conclusions. The two prospective studies demonstrate additional evidence, but are limited by the relatively low number of patients included. Nevertheless, all the available data suggest the effectiveness of adjunctive treatment with leflunomide in GCA patients.

Our study was limited by its single-center, open-label design and the smaller size of the control group (glucocorticoid-only group); however, it was the result of a previously acquired positive experience with the use of leflunomide at our center. Due to its limitations, the results and conclusions of our study should be interpreted with caution. Nevertheless, we have presented the largest cohort of GCA patients treated with leflunomide to date. The main strength of our study is its prospective nature and external validity by means of the prospective inclusion of an unselected real-world GCA population, and the fact it followed a predefined systematic treatment regimen and follow-up strategy. Despite the limitations, this study significantly contributes to the growing knowledge of the effectiveness of leflunomide and its steroid-sparing effect in patients with GCA.

In conclusion, in this prospective single-center, open-label study, by adding leflunomide to the EULAR-recommended glucocorticoid regimen in GCA treatment, we demonstrated the encouraging potential of leflunomide to safely and effectively reduce the relapse rate at a lower cumulative glucocorticoid dose in over three quarters of GCA patients in our cohort.

Our experiences with leflunomide should be further verified in a randomized control trial.

Data availability statement

The datasets analysed in the current study are available from the corresponding author upon reasonable request.

Ethics statement

The studies involving human participants were reviewed and approved by Republic of Slovenia National Medical Ethics Committee, Ljubljana, Slovenia. The patients/participants provided their written informed consent to participate in this study.

Author contributions

JK and AH contributed to the acquisition of data. AH analyzed and interpreted data. MT and ŽR helped revise the manuscript. All authors have read and approved the manuscript for submission.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised international chapel hill consensus conference nomenclature of vasculitides. *Arthritis Rheum.* (2013) 65:1–11. doi: 10.1002/art.37715

2. Patil P, Williams M, Maw WW, 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:S-103-6.

3. Diamantopoulos AP, 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? *Rheumatology.* (2016) 55:66–70. doi: 10.1093/rheumatology/kev289

4. Hocevar A, Rotar Z, Jese R, Semrl SS, Pizem J, Hawlina M, et al. Do early diagnosis and glucocorticoid treatment decrease the risk of permanent visual loss and early relapses in giant cell arteritis. *Medicine.* (2016) 95:e3210. doi: 10.1097/MD.0000000000003210

5. Hellmich B, Águeda AF, Monti S, Luqmani R. Treatment of giant cell arteritis and takayasu arteritis—current and future. *Curr Rheumatol Rep.* (2020) 22:84. doi: 10.1007/s11926-020-00964-x

6. Restuccia G, Boiardi L, Cavazza A, Catanoso M, Macchioni P, Muratore F, et al. Long-term remission in biopsy proven giant cell arteritis: a retrospective cohort study. *J Autoimmun.* (2017) 77:39–44. doi: 10.1016/j.jaut.2016.10.002

7. Wilson JC, Sarsour K, Collinson N, Tuckwell K, Musselman D, Klearman M, et al. Incidence of outcomes potentially associated with corticosteroid therapy in patients with giant cell arteritis. *Semin Arthritis Rheum.* (2017) 46:650–6. doi: 10.1016/j.semarthrit.2016.10.001

8. Serling-Boyd N, Stone JH. Recent advances in the diagnosis and management of giant cell arteritis. *Curr Opin Rheumatol.* (2020) 32:201–7. doi: 10.1097/BOR.0000000000000700

9. Mahr AD, Jover JA, Spiera RF, Hernández-García C, Fernández-Gutiérrez B, LaValley MP, et al. Adjunctive methotrexate for treatment of giant cell arteritis: an individual patient data meta-analysis. *Arthritis Rheum.* (2007) 56:2789–97. doi: 10.1002/art.22754

10. 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) 46:1309–18. doi: 10.1002/art.10262

11. Metzler C. Maintenance of remission with leflunomide in Wegener's granulomatosis. *Rheumatology.* (2003) 43:315–20. doi: 10.1093/rheumatology/keh009

12. de Souza AWS, de Almeida Agustinelli R, de Cinque Almeida H, Oliveira PB, Pinheiro FAG, Oliveira ACD, et al. Leflunomide in takayasu arteritis-a long term observational study. *Rev Bras Reumatol.* (2016) 56:371–5. doi: 10.1016/j.rbre.2016.02.003

13. Kirsch BM, Zeyda M, Stuhlmeier K, Grisar J, Smolen JS, Watschinger B, et al. The active metabolite of leflunomide, A77 1726, interferes with dendritic cell function. *Arthritis Res Ther.* (2005) 7:R694. doi: 10.1186/ar1727

14. Martinez-Taboada VM, Alvarez L, RuizSoto M, Marin-Vidalled MJ, Lopez-Hoyos M. Giant cell arteritis and polymyalgia rheumatica: role of cytokines in the pathogenesis and implications for treatment. *Cytokine.* (2008) 44:207–20. doi: 10.1016/j.cyto.2008.09.004

15. Hočevar A, Ješe R, Rotar Ž, Tomšič M. Does leflunomide have a role in giant cell arteritis? An open-label study. *Clin Rheumatol.* (2019) 38:291–6. doi: 10.1007/s10067-018-4232-x

16. Tengesdal S, Diamantopoulos A, Myklebust G. Leflunomide versus methotrexate in treatment of giant cell arteritis: comparison of efficacy, safety, and drug survival. *Scand J Rheumatol.* (2019) 48:333–5. doi: 10.1080/03009742.2019.1575980

17. Diamantopoulos AP, Hetland H, Myklebust G. Leflunomide as a corticosteroid-sparing agent in giant cell arteritis and polymyalgia rheumatica: a case series. *Biomed Res Int.* (2013) 2013:1–3. doi: 10.1155/2013/120638

18. Das S, Goswami RP, Sinha D, Ghosal A, Datta A, Sarkar S. Efficacy of leflunomide as a steroid-sparing agent in treatment of Indian giant cell arteritis patients: a 2-year follow-up study. *Int J Rheum Dis.* (2022) 25:650–8. doi: 10.1111/1756-185X.14319

19. Mustapha N, Barra L, Carette S, Cuthbertson D, Khalidi NA, Koening CL, et al. Efficacy of leflunomide in the treatment of vasculitis. *Clin Exp Rheumatol.* (2021) 39:114–8. doi: 10.55563/clinexprheumatol/ve38dj

20. Tomelleri A, Coath F, Sebastian A, Prieto-Pena D, Kayani A, Mo J, et al. Long-term efficacy and safety of leflunomide in large-vessel giant cell arteritis. *JCR J Clin Rheumatol.* (2022) 28:e297–300. doi: 10.1097/RHU.0000000000001703

21. 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 Pract.* (2012) 66:906–9. doi: 10.1111/j.1742-1241.2012.02981.x

22. Hunder GG, Bloch DA, Michel BA, Stevens MB, Arend WP, Calabrese LH, et al. The American college of rheumatology 1990 criteria for the classification of giant cell arteritis. *Arthritis Rheum.* (1990) 33:1122–8. doi: 10.1002/art.1780330810

23. Hellmich B, Agueda A, Monti S, Buttgereit F, de Boysson H, Brouwer E, et al. 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. *Ann Rheum Dis.* (2020) 79:19–30. doi: 10.1136/annrheumdis-2019-215672

24. 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) 68:318–23. doi: 10.1136/ard.2008.088351

25. Yates M, Loke YK, Watts RA, MacGregor AJ. Prednisolone combined with adjunctive immunosuppression is not superior to prednisolone alone in terms of efficacy and safety in giant cell arteritis: meta-analysis. *Clin Rheumatol.* (2014) 33:227–36. doi: 10.1007/s10067-013-2384-2

26. Litinsky I, Paran D, Levartovsky D, Wigler I, Kaufman I, Yaron I, et al. The effects of leflunomide on clinical parameters and serum levels of IL-6, IL-10, MMP-1 and MMP-3 in patients with resistant rheumatoid arthritis. *Cytokine.* (2006) 33:106–10. doi: 10.1016/j.cyto.2005.12.009

27. Lillegraven S, Paulshus Sundlisæter N, Aga A-B, Sexton J, Olsen IC, Fremstad H, et al. Effect of half-dose vs stable-dose conventional synthetic disease-modifying antirheumatic drugs on disease flares in patients with rheumatoid arthritis in remission. *JAMA.* (2021) 325:1755. doi: 10.1001/jama.2021.4542

28. Alcorn N, Saunders S, Madhok R. Benefit-risk assessment of leflunomide: an appraisal of leflunomide in rheumatoid arthritis 10 years after licensing. *Drug Saf.* (2009) 32:1123–34. doi: 10.2165/11316650-000000000-00000

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EDITED BY
Andreas P. Diamantopoulos,
Akershus University Hospital, Norway

REVIEWED BY
Mark Matza,
Massachusetts General Hospital and Harvard Medical School, United States
Hubert De Boysson,
Centre Hospitalier Universitaire de Caen, France

*CORRESPONDENCE
Olivier Espitia
olivier.espitia@chu-nantes.fr

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Inter and intra-observer agreement of arterial wall contrast-enhanced ultrasonography in giant cell arteritis

Olivier Espitia[1]*, Olivier Robin[1], Jeanne Hersant[2], Christophe Roncato[3], Arthur Théry[4], Marie-Anne Vibet[5], Giovanni Gautier[1], Alizée Raimbeau[1] and François-Xavier Lapébie[4]

[1]Nantes Université, Centre Hospitalier Universitaire (CHU) Nantes, Department of Internal and Vascular Medicine, Nantes, France, [2]Department of Vascular Medicine, Centre Hospitalier Universitaire (CHU) Angers, Angers, France, [3]Department of Vascular Medicine, Centre Hospitalier Saint-Louis, La Rochelle, France, [4]Department of Vascular Medicine, Centre Hospitalier Universitaire (CHU) Toulouse, Toulouse, France, [5]Department of Biostatistics, Centre Hospitalier Universitaire (CHU) Nantes, Nantes, France

Objective: The aim of this study was to analyze inter- and intra-observer agreement for contrast-enhanced ultrasonography (CEUS) for monitoring disease activity in Giant Cell Arteritis (GCA) in the wall of axillary arteries, and common carotid arteries.

Methods: Giant cell arteritis patients have CEUS of axillary arteries and common carotid. These images were rated by seven vascular medicine physicians from four hospitals who were experienced in duplex ultrasonography of GCA patients. Two weeks later, observers again rated the same images. GCA patients were recruited in from December 2019 to February 2021. An analysis of the contrast of the ultrasound images with a gradation in three classes (grade 0, 1, and 2) was performed. Grade 0 corresponds to no contrast, grade 1 to moderate wall contrast and grade 2 to intense contrast. A new analysis in 2 classes: positive or negative wall contrast; was then performed on new series of images.

Results: Sixty arterial segments were evaluated in 30 patients. For the three-class scale, intra-rater agreement was substantial: κ 0.70; inter-rater agreement was fair: κ from 0.22 to 0.27. Thirty-four videos had a wall thickness of less than 2 mm and 26 videos had a wall thickness greater than 2 mm. For walls with a thickness lower than 2 mm: intra-rater agreement was substantial: κ 0.69; inter-rater agreement was fair: κ 0.35. For walls with a thickness of 2 mm or more: intra-rater agreement was substantial: κ 0.53; inter-rater agreement was fair: κ 0.25. For analysis of parietal contrast uptake in two classes: inter-rater agreement was fair to moderate: κ from 0.35 to 0.41; and for walls with a thickness of 2 mm or more: inter-rater agreement was fair to substantial κ from 0.22 to 0.63.

Conclusion: The visual analysis of contrast uptake in the wall of the axillary and common carotid arteries showed good intra-rater agreement in GCA patients. The inter-rater agreement was low, especially when contrast was analyzed in three classes. The inter-rater agreement for the analysis in two classes was also low. The inter-rater agreement was higher in two-class analysis for walls of 2 mm thickness or more.

KEYWORDS

contrast-enhanced ultrasonography (CEUS), giant cell arteritis–large-vessel, agreement, giant cell arteritis, large-vessel vasculitis (LVV)

Introduction

Giant cell arteritis (GCA) is the most common vasculitis in elderly people, with large-vessel vasculitis (LVV) involvement in slightly more than half of the GCA cases, such as the aorta and its branches particularly the axillary artery (1–3). GCA is characterized by an arterial wall inflammatory process within the vessel wall leading to structural arterial wall alterations from mild thickening until arterial occlusion, with late complications as aneurysm (4). Assessment of arterial wall inflammatory activity is important for monitoring GCA activity. Traditionally, the GCA evaluation was based on the clinical signs with monitoring of biological inflammatory markers such as erythrocyte sedimentation rate or C-reactive protein (CRP), but with the use of interleukin-6 receptor blockers, these biological parameters are becoming less informative. More recently, imaging by computed tomography (CT) scan, positron emission tomography (PET/CT) scan, color Doppler ultrasonography (CDUS) or magnetic resonance imaging (MRI), have become very important in the diagnosis of GCA but their use for the follow-up, in particular to evaluate the LVV activity of the disease, remains to be specified. Follow-up imaging data are heterogeneous, mainly because of a lack of standardization in the interpretation of these images.

Contrast-enhanced ultrasound (CEUS) was developed for a better vascular visualization. This examination is an ultrasound in B-mode, associated with an injection of ultrasound contrast. It consists of microbubbles of weakly soluble sulfur hexafluoride gas stabilized by a phospholipid and palmitic acid envelope, which allows an increase in circulation time after intravenous injection and therefore an increase in the duration of the examination (5). These microbubbles remain strictly localized to the vascular compartment. They are eliminated within 15 min after the injection.

Contrast-enhanced ultrasound was developed to improve the visualization of the vessel lumen and to identify unstable carotid plaques at an increased risk of stroke. These unstable plaques are characterized by the presence of intraplaque inflammation, leading to the formation of neovascularization that are likely to rupture, which may result in plaque fissure, thrombus formation, and stroke (5, 6). Injection of an ultrasound contrast medium allows ultrasound visualization of microbubbles circulating in these neo-vessels. CEUS is also used to improve vascular visualization in aortic prosthesis monitoring and in digestive vascular imaging.

In GCA, arteries could be evaluated using B-mode and CDUS imaging. Typical signs of GCA are circumferential, homogeneous, hypo-echogenic wall thickening ("halo sign") or compression sign for temporal arteritis (7–9). The intima-media thickness (IMT) $\geq$1 mm cutoff value, in the axillary artery has sensitivity and specificity values of 96.1–100% for GCA but 6 months after GCA treatment, approximately 50% of the patients had persistent arterial thickening despite normalization of biological inflammatory markers and the absence of clinical symptoms (10–12). To improve wall thickening analysis, CEUS could be used for vascular imaging, especially for patients with a persistent thickened vessel wall in large-vessels.

Studies using CEUS in patients with GCA or Takayasu arteritis (TA) describe uptake of ultrasound contrast agent into the vessel wall in active vasculitis (11–16). Previously published studies with CEUS in LVV used a semi-quantitative score with three-class scale (6). CEUS could detect an increase in the vascularization of the wall of these arteries, which seems to correlate with the activity (11, 17, 18). Few studies have been performed in GCA patients and they most often report GCA patients associated with TA patients. A pilot study of seven patients with TA (n = 5) or GCA (n = 2) has evaluated CDUS and CEUS of the carotid arteries (14). Of the 14 carotid arteries examined, 50% had lesions on CDUS (parietal thickening), and 64% had neovascularization of the wall on CEUS. CEUS was positive on both carotid arteries in one patient while the CDUS was negative, and conversely, parietal thickening was noted on one carotid artery in one patient on CDUS without contrast uptake on CEUS. Another study compared CEUS and PET/CT of the carotid arteries in a series of 31 consecutive patients with TA (n = 14), or GCA with LLV on PET/CT (n = 17) (15). In 10 patients, PET/CT revealed carotid arteries FDG uptake considered as active disease. Using the PET/CT as a

reference, the sensitivity and specificity of carotid CEUS were 100 and 92%, respectively. Inflammation revealed by PET/CT and neovascularization of the arterial wall revealed by CEUS were correlated (15).

Thus, up to date, the biggest challenge in CDUS as in CEUS is the lack of quantitative, reliable, and effective measures to evaluate disease activity in GCA and monitoring of treatment response.

The objective of this study was to investigate the reliability (consistency and reproducibility) of arterial wall CEUS in GCA with semi-quantitative visual analysis by comparing the classification of different experts on sets of ultrasound loops (inter-rater association) and on experts' own repeated ratings (intra-rater association).

Materials and methods

Inclusion criteria

Inclusion criteria were GCA patients, with American College of Rheumatology (ACR) criteria (19), or age >50 years and CRP >10 mg/L and vasculitis on imaging: ultrasound, MRI, CT or PET/CT (20–23). This study included patients with large-vessel involvement with increased IMT ≥0.8 mm at the axillary or common carotid arteries on CDUS. Patients were included from December 2019 to February 2021.

Contrast-enhanced ultrasound examination

Contrast-enhanced ultrasound was performed on a Toshiba Aplio 400 ultrasound machine (Canon Medical Systems, Europe) with a L11-4 linear array probe according to the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) guidelines (24). The common carotid artery and axillary arteries were assessed by the same experienced physicians. The ultrasound examination was performed with the patient in the supine position. For each patient, the bilateral carotid and axillary arteries were examined and the wall thickness (IMT) of the common carotid artery and axillary arteries were measured.

The mechanical index was between 0.06 and 0.09. The instrument parameters were kept consistent for all patients. The gray scale was automatically adapted. The maximum IMT was measured using CDUS, and the most prominently thickened vessel segment was chosen based on the accessibility to all parts of the vessel wall. CEUS was performed at the thickest site of the common carotid or axillary artery. Micro Flow Imaging (MFI) mode was used for recording image loops.

Each contrast agent infusion was followed by a saline flush with 10 ml of NaCl 0.9% solution. After injection of 2.5 mL of ultrasound contrast agent (SonoVue, Bracco S.p.A., Milan, Italy), a continuous ultrasound video was recorded over 60 s, and the image loops were stored on an ultrasound machine. Afterward, the recorded movies were analyzed by a real time examination.

Study design

Images were analyzed by experienced seven vascular physicians (named thereafter observers) from three university hospitals and one general hospital. Consensus meetings were held, a first meeting to specify the evaluation method and comparing the analysis data obtained by the evaluation of three experienced investigators, then each observer analyzed 10 loops of training images and after analysis of the data a second meeting to adjust and harmonize the evaluations was held; then each operator analyzed 4 series of 30 image loops. An initial three-class analysis was performed. The degree of neovascularization at the thickening wall on CEUS was defined as follows (**Figure 1**): grade 0, no vascularization, representing no moving microbubbles in the thickened artery lesions; grade 1, limited or moderate vascularization, representing limited or moderate visible appearance of microbubbles in the thickened artery lesions; and grade 2, severe vascularization, representing extensive wall vascularization with a clear visible appearance of microbubbles (**Supplementary Video 1**) (14). A second two-class analysis was then performed, describing no wall contrast or arterial wall contrast. The order of reviewing the image sets was different between each series; the review of each image set was performed with at least a 2-week interval to reduce recall bias. The investigators were blinded to clinical and biological data.

Ethics

This study was conducted in compliance with the Declaration of Helsinki principles and received ethics approval by the local ethics committee of the University Hospital of Nantes. Each patient included in this study received written information and no patient objected to this study. No written informed consent was needed by the ethics committee because of the retrospective study design (French public health code article: L 1121-1).

Statistical analysis

Agreement and association measures are used to quantify the degree of consistency between experts' categorical (e.g., binary or ordinal) ratings. For ordered ratings, measures of association are recommended since diminishing credit is assigned for pairs of ratings on the same patient's test

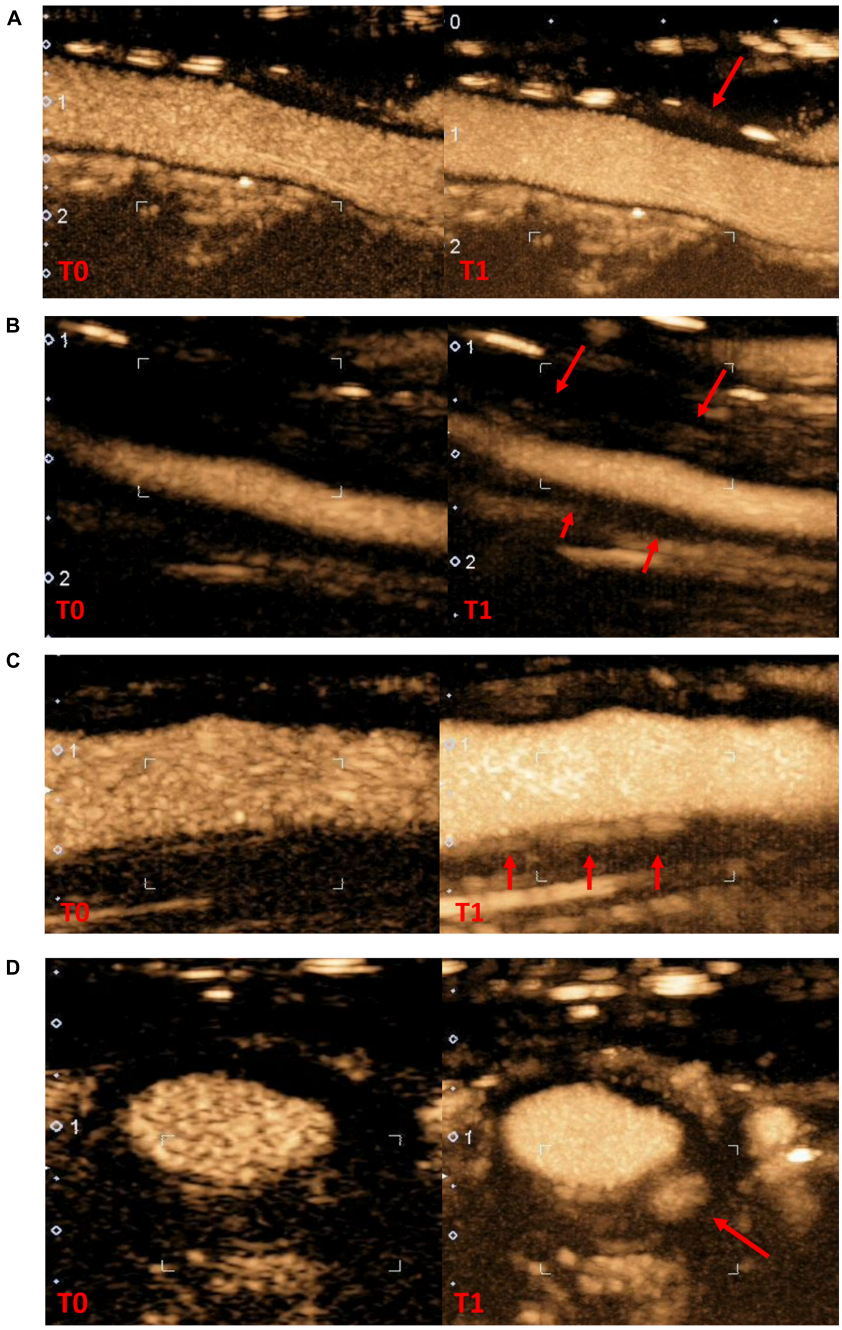

FIGURE 1
Contrast-enhanced ultrasonography in arterial wall in giant cells arteritis patients **(A),** no contrast-enhanced **(B)**, grade 1 moderate contrast-enhanced **(C)**, grade 2 high contrast-enhanced in longitudinal section **(D)**, grade 2 contrast-enhanced in cross section (T0: wall reference at the start of contrast infusion; T1: wall contrast at the end of the recording, red arrow specific arterial wall thickening area where contrast-enhanced was evaluated).

result which are similar but not in full agreement. Measures of agreement are focusing on assessing the levels of exact concordance (i.e., where raters assign the exact same category to a subject's test result), whereas measures of association also take into account the degrees of disagreement among raters' classifications.

In this design, a group of raters scored a set of patients' test results twice, leading to dependencies between classifications. Hence we applied the modeled based kappa evaluation developed by Nelson et al. that provides an overall evaluation (consistency and reproducibility) of the association among multiple raters' paired scores of patients' imaging results, at two

TABLE 1 Inter and intra-observer agreement of arterial wall contrast-enhanced ultrasonography in three-class scale analysis.

Measure of association	Estimated kappa	(95% CI)
Intra-rater	0.70	(0.65; 0.75)
Inter-rater (1st evaluation)	0.27	(0.19; 0.35)
Inter-rater (2nd evaluation)	0.22	(0.15; 0.29)

TABLE 2 Inter-observer agreement of arterial wall contrast-enhanced ultrasonography in two-class scale analysis (CI: *confidence interval*).

Measure of agreement	Estimated kappa	(95% CI)
Intra-rater	0.56	(0.43; 0.69)
Inter-rater (1st evaluation)	0.35	(0.21; 0.57)
Inter-rater (2nd evaluation)	0.41	(0.25; 0.60)

points of time (25, 26). As no intervention was planned between the two points of time, the consistency between rater's paired assessments is determined by the intra-rater association whereas the reproducibility is at tested by the inter-rater association.

Statistical analysis Inter- and intra-observer agreements (or association) were interpreted by the Landis and Koch interpretation: 0.21–0.40: fair; 0.41–0.60: moderate, 0.61–0.80: substantial; ≥0.81: almost perfect.

Results

We included 30 patients with newly diagnosed or known GCA with LVV of the axillary and/or carotid arteries. The mean age of all included patients was 75.7 ± 5.7 years. The patients were predominantly female: 63.3% (19 females). The mean wall thickness was 2.1 ± 1.1 mm.

For the whole of the observers, the mean number of views of each ultrasound loop was 4.4 ± 1.1 in three-class scale analyses. Inter and intra−observer agreements of arterial wall contrast-enhanced ultrasonography in three-class analysis are summarized in Table 1. The intra-observer association is high (0.7), indicating substantial consistency between both evaluation series at time 1 and time 2 by each observer. The inter-observer association at time 1 is low (0.27) and at time 2 is even lower (0.22). This indicates that consistency between raters is no more than fair.

The agreement of arterial wall contrast in two classes is presented in Table 2. The two-class assessment modestly increases inter-observer agreements, moving from fair to moderate agreement. However, the intra-rater agreement is lower than in the three-class evaluation, indicating a lesser consistency in the evaluation between two views of ultrasound loops.

Out of the 30 image loops, 13 had an arterial wall thickness greater than 2 mm. Inter and intra−observer agreement of arterial wall contrast-enhanced ultrasonography in three-class or two-class analysis, according to an arterial wall thickness less or greater than or equal to 2 mm are presented in Tables 3,4. In the cases, the intra-observer association ranges from 0.53 to 0.69, indicating moderate to substantial consistency between both evaluation series by each observer. The inter-observer agreements were fair ranging from 0.25 to 0.35 in the three-class analysis. In the two-class analysis, they showed a great variability especially for walls <2 mm.

TABLE 3 Inter and intra-observer agreement of arterial wall contrast-enhanced ultrasonography in three-class scale analysis according to an arterial wall thickness (CI: *confidence interval*).

Measure of association	Estimated kappa	(95% CI)
Arterial wall thickness <2 mm		
Intra-rater	0.69	(0.59; 0.79)
Inter-rater (1st evaluation)	0.35	(0.20; 0.50)
Inter-rater (2nd evaluation)	0.35	(0.20; 0.50)
Arterial wall thickness ≥2 mm		
Intra-rater	0.53	(0.46; 0.60)
Inter-rater (1st evaluation)	0.25	(0.09; 0.41)
Inter-rater (2nd evaluation)	0.25	(0.09; 0.41)

TABLE 4 Inter and intra-observer agreement of arterial wall contrast-enhanced ultrasonography in two-class scale analysis according to an arterial wall thickness (CI: *confidence interval*).

Measure of association	Estimated kappa	(95% CI)
Arterial wall thickness <2 mm		
Intra-rater	0.56	(0.42; 0.70)
Inter-rater (1st evaluation)	0.36	(0.19; 0.66)
Inter-rater (2nd evaluation)	0.02	(−0.09; 0.27)
Arterial wall thickness ≥2 mm		
Intra-rater	0.57	(0.45; 0.68)
Inter-rater (1st evaluation)	0.22	(0.05; 0.44)
Inter-rater (2nd evaluation)	0.63	(0.59; 0.86)

The physician's experience did not affect inter- and intra-observer agreements (Tables 5,6). However, the CEUS is globally little performed in GCA, thus none of the physicians has performed more than 300 CEUS in GCA to evaluate disease activity in arterial wall.

Discussion

This multicenter study is the first to investigate inter- and intra-observer agreements of arterial wall contrast in GCA with visual assessment of contrast. In this study, intra-observer agreement in the analysis of arterial parietal contrast uptake in GCA was good with an analysis performed in three-class scale. On the other hand, the inter-observer agreement is fair with κ between 0.22 and 0.27 for an analysis in three-class scale, the inter-observer agreement is slightly better from fair to

TABLE 5 Inter and intra-observer agreement of arterial wall contrast-enhanced ultrasonography in three-class scale analysis according to physician's experience (CI: *confidence interval*).

Measure of association	Estimated kappa	(95% CI)
Physician with more than 5 years of experience		
Intra-rater	0.68	(0.66; 0.70)
Inter-rater (1st evaluation)	0.35	(0.32; 0.38)
Inter-rater (2nd evaluation)	0.36	(0.33; 0.39)
Physician with less than 5 years of experience		
Intra-rater	0.72	(0.70; 0.73)
Inter-rater (1st evaluation)	0.39	(0.36; 0.42)
Inter-rater (2nd evaluation)	0.38	(0.35; 0.41)

TABLE 6 Inter and intra-observer agreement of arterial wall contrast-enhanced ultrasonography in two-class scale analysis according to physician's experience (CI: *confidence interval*).

Measure of association	Estimated kappa	(95% CI)
Physician with more than 5 years of experience		
Intra-rater	0.51	(0.38; 0.65)
Inter-rater (1st evaluation)	0.07	NA
Inter-rater (2nd evaluation)	0.42	NA
Physician with less than 5 years of experience		
Intra-rater	0.62	(0.47; 0.76)
Inter-rater (1st evaluation)	0.68	NA
Inter-rater (2nd evaluation)	0.55	NA

moderate when the analysis is performed in 2-class scale with κ between 0.35 and 0.41.

Parietal thickening appears to be important to consider in the visual analysis of contrast uptake since inter-observer agreement in the two-category analysis showed higher agreement rates when the wall had a thickness of ≥2 mm. Thus, it is possible that the performance of semi-quantitative contrast score analysis is different in GCA compared with TA because wall thickenings in TA are often much greater than in GCA (12–15). The thicker the wall the more concordant the assessment between observers, however, it remains insufficiently reproducible in this study to take a decision for therapeutic modification.

The results of this study discuss the value of visual assessment of wall contrast uptake in view of the poor inter-observer agreement. Thus, a study of contrast uptake by quantitative methods seems more interesting during LVV. Some authors have proposed other ways of analyzing contrast intake. As such, Bergner et al. used the difference in contrast-enhanced areas between lumen contrast and arterial wall contrast for the study of contrast uptake (16). To better analyze the arterial wall in the LVV, an automated contrast analysis method with digital detection tools should be validated. For CEUS, Giordana et al. reported a lowering of the gray scale median of the common carotid wall under steroid treatment in TA (27). If CEUS interpretation is efficient and reproducible, it could be used in routine clinical practice; it will make monitoring much easier to repeat, safer, faster, and much more cost-effective than MRI or PET/CT. Thus, CEUS could be a good method to monitor GCA activity with large-vessels involvement. The results highlight the need to increase the reproducibility of CEUS as the inter-observer agreement was disappointing. If these results are confirmed, visual interpretation of CEUS cannot be recommended for LVV evaluation in routine practice. It does not seem appropriate to decide on a treatment change based on a visual analysis of the CEUS.

The variability of ultrasound should be put into perspective with inter-observer agreement variabilities for other imaging techniques. To our knowledge, there is no study that has investigated the concordance between observers for CT in GCA. For PET/CT, visual grading system analysis in four classes with liver uptake as reference had good inter observer agreement with κ from 0.79 to 0.96 (28). In CDUS, the main inter-observer agreement data were performed on the temporal arteries and axillary arteries. For the diagnosis of temporal arteritis, "halo" and "compression" signs were the main CDUS patterns for GCA diagnosis. For the halo sign, the agreement between the observers evaluated on images was 0.95 and the agreement of the halo sign on video loop was 0.84 (9). Compression sign for the diagnosis of temporal arteritis had an excellent inter-observer κ:0.83–0.92 (9, 29). For chronic wall modifications of axillary arteries in GCA, the CDUS inter-reader reliability was κ 0.79–0.80 for and κ was 0.88 for intra-reader agreement (30).

The strengths of this study are the multicenter image analysis, image loops were performed in a single center with an identical image acquisition protocol, a blinded analysis of clinical biological data and imaging such as PET/CT. The limitations of this study include the small number of patients and the absence of a probe motion reduction system to limit motion artifacts that alter the interpretation of image loops with the MFI mode. Concerning the experience acquisition of the physician, CEUS is mainly performed in a few expert centers, unlike GCA diagnostic or follow-up CDUS, because few patients with artery wall thickenings are eligible for CEUS and very few centers realize CEUS. Acquiring experience in performing and interpreting the CEUS seems to us to be more difficult to obtain than mastering the compression sign or the halo sign with the CDUS. Thus, the development of software to assist interpretation seems fundamental to have a better reproducibility of results and to have a quantitative evaluation of the contrast uptake.

Conclusion

This multicenter study showed that the intra-observer agreement for CEUS was good for the semi-quantitative visual

analysis. In contrast, inter-observer agreement was poor for semi-quantitative visual analysis and moderately improved when contrast uptake analysis was binary. A significant parietal thickening improved inter-observer agreement in binary analysis. Prospective studies with digital and automated CEUS analysis should be performed to clarify the interest of CEUS in the follow-up of GCA.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Groupe Nantais d'Ethique dans le Domaine de la Santé. Written informed consent for participation was not required for this study in accordance with the National Legislation and the institutional requirements.

Author contributions

OE, OR, and F-XL: data collection analysis and interpretation, and drafting of the manuscript. JH, OR, F-XL, AT, AR, GG, and OE: data collection and critical review. OE, OR, and M-AV: methodology, analysis, and interpretation of data. OE: study concept and design, data collection, analysis and interpretation, drafting of the manuscript, and supervision. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.1042366/full#supplementary-material

SUPPLEMENTARY VIDEO 1
Grade 2 contrast-enhanced registration loop of an axillary artery in longitudinal section; left window with grade 2 contrast enhancement with significant thickening of the arterial wall on the right side of the image. On the right window, B-mode video of the same artery, registration was performed automatically at the same time.

References

1. Agard C, Barrier J-H, Dupas B, Ponge T, Mahr A, Fradet G, et al. Aortic involvement in recent-onset giant cell (temporal) arteritis: a case-control prospective study using helical aortic computed tomodensitometric scan. *Arthritis Rheum.* (2008) 59:670–6. doi: 10.1002/art.23577

2. Prieto-González S, Arguis P, García-Martínez A, Espígol-Frigolé G, Tavera-Bahillo I, Butjosa M, et al. Large vessel involvement in biopsy-proven giant cell arteritis: prospective study in 40 newly diagnosed patients using CT angiography. *Ann Rheum Dis.* (2012) 71:1170–6. doi: 10.1136/annrheumdis-2011-200865

3. Blockmans D. The use of (18F) fluoro-deoxyglucose positron emission tomography in the assessment of large vessel vasculitis. *Clin Exp Rheumatol.* (2003) 21:S15–22.

4. Muratore F, Kermani TA, Crowson CS, Koster MJ, Matteson EL, Salvarani C, et al. Large-vessel dilatation in giant cell arteritis: a different subset of disease? *Arthritis Care Res.* (2018) 70:1406–11. doi: 10.1002/acr.23498

5. Baud JM, Luong S, Rouyer O, Maurizot A, Gautier C. Pour le groupe de travail sur l'échographie de contraste carotidienne. [Contribution of contrast enhanced ultrasonography in the characterization of carotid lesions]. *J Med Vasc.* (2017) 42:301–14. doi: 10.1016/j.jdmv.2017.06.003

6. Staub D, Partovi S, Schinkel AFL, Coll B, Uthoff H, Aschwanden M, et al. Correlation of carotid artery atherosclerotic lesion echogenicity and severity at standard US with intraplaque neovascularization detected at contrast-enhanced US. *Radiology.* (2011) 258:618–26. doi: 10.1148/radiol.10101008

7. Czihal M, Zanker S, Rademacher A, Tatò F, Kuhlencordt PJ, Schulze-Koops H, et al. Sonographic and clinical pattern of extracranial and cranial giant cell arteritis. *Scand J Rheumatol.* (2012) 41:231–6. doi: 10.3109/03009742.2011.641581

8. Hellmich B, Agueda A, Monti S, Buttgereit F, de Boysson H, Brouwer E, et al. 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. *Ann Rheum Dis.* (2020) 79:19–30. doi: 10.1136/annrheumdis-2019-215672

9. Chrysidis S, Duftner C, Dejaco C, Schäfer VS, Ramiro S, Carrara G, et al. Definitions and reliability assessment of elementary ultrasound lesions in giant cell arteritis: a study from the OMERACT large vessel vasculitis ultrasound working group. *RMD Open.* (2018) 4:e000598. doi: 10.1136/rmdopen-2017-000598

10. Pérez López J, Solans Laqué R, Bosch Gil JA, Molina Cateriano C, Huguet Redecilla P, Vilardell Tarrés M. Colour-duplex ultrasonography of the temporal and ophthalmic arteries in the diagnosis and follow-up of giant cell arteritis. *Clin Exp Rheumatol.* (2009) 27:S77–82.

11. Ma L-Y, Li C-L, Ma L-L, Cui X-M, Dai X-M, Sun Y, et al. Value of contrast-enhanced ultrasonography of the carotid artery for evaluating disease activity in takayasu arteritis. *Arthritis Res Ther.* (2019) 21:24. doi: 10.1186/s13075-019-1813-2

12. Lottspeich C, Dechant C, Köhler A, Tischler M, Treitl KM, Treitl M, et al. Assessment of disease activity in takayasu arteritis: potential role of contrast-enhanced ultrasound. *Ultraschall Med.* (2019) 40:638–45. doi: 10.1055/a-0817-5423

13. Wang Y, Wang Y-H, Tian X-P, Wang H-Y, Li J, Ge Z-T, et al. Contrast-enhanced ultrasound for evaluating arteritis activity in takayasu arteritis patients. *Clin Rheumatol.* (2020) 39:1229–35. doi: 10.1007/s10067-019-04698-9

14. Schinkel AFL, van den Oord SCH, van der Steen AFW, van Laar JAM, Sijbrands EJG. Utility of contrast-enhanced ultrasound for the assessment of the carotid artery wall in patients with takayasu or giant cell arteritis. *Eur Heart J Cardiovasc Imaging.* (2014) 15:541–6. doi: 10.1093/ehjci/jet243

15. Germanò G, Macchioni P, Possemato N, Boiardi L, Nicolini A, Casali M, et al. Contrast-enhanced ultrasound of the carotid artery in patients with large vessel vasculitis: correlation with positron emission tomography findings. *Arthritis Care Res.* (2017) 69:143–9. doi: 10.1002/acr.22906

16. Bergner R, Splitthoff J, Wadsack D. Use of contrast-enhanced ultrasound sonography in giant cell arteritis: a proof-of-concept study. *Ultrasound Med Biol.* (2022) 48:143–8. doi: 10.1016/j.ultrasmedbio.2021.09.019

17. Czihal M, Lottspeich C, Hoffmann U. Ultrasound imaging in the diagnosis of large vessel vasculitis. *VASA Z Gefasskrankheiten.* (2017) 46:241–53. doi: 10.1024/0301-1526/a000625

18. Dong Y, Wang Y, Wang Y, Tian X, Li J, Yang Y, et al. Ultrasonography and contrast-enhanced ultrasound for activity assessment in 115 patients with carotid involvement of takayasu arteritis. *Mod Rheumatol.* (2022). [Epub ahead of print]. doi: 10.1093/mr/roac107

19. Hunder GG, Bloch DA, Michel BA, Stevens MB, Arend WP, Calabrese LH, et al. The American college of rheumatology 1990 criteria for the classification of giant cell arteritis. *Arthritis Rheum.* (1990) 33:1122–8.

20. Berthod PE, Aho-Glélé S, Ornetti P, Chevallier O, Devilliers H, Ricolfi F, et al. CT analysis of the aorta in giant-cell arteritis: a case-control study. *Eur Radiol.* (2018) 28:3676–84. doi: 10.1007/s00330-018-5311-8

21. Monti S, Floris A, Ponte CB, Schmidt WA, Diamantopoulos AP, Pereira C, et al. The proposed role of ultrasound in the management of giant cell arteritis in routine clinical practice. *Rheumatol Oxf Engl.* (2017) 57:112–9. doi: 10.1093/rheumatology/kex341

22. Espitia O, Schanus J, Agard C, Kraeber-Bodéré F, Hersant J, Serfaty J-M, et al. Specific features to differentiate giant cell arteritis aortitis from aortic atheroma using FDG-PET/CT. *Sci Rep.* (2021) 11:17389. doi: 10.1038/s41598-021-96923-2

23. Slart RHJA, Writing group, Reviewer group, Members of EANM Cardiovascular, Members of EANM Infection and Inflammation, Members of Committees, et al. FDG-PET/CT(A) imaging in large vessel vasculitis and polymyalgia rheumatica: joint procedural recommendation of the EANM, SNMMI, and the PET interest group (PIG), and endorsed by the ASNC. *Eur J Nucl Med Mol Imaging.* (2018) 45:1250–69. doi: 10.1007/s00259-018-3973-8

24. Sidhu PS, Cantisani V, Dietrich CF, Gilja OH, Saftoiu A, Bartels E, et al. The EFSUMB guidelines and recommendations for the clinical practice of contrast-enhanced ultrasound (ceus) in non-hepatic applications: update 2017 (long version). *Ultraschall Med.* (2018) 39:e2–44. doi: 10.1055/a-0586-1107

25. Nelson KP, Edwards D. Measures of agreement between many raters for ordinal classifications. *Stat Med.* (2015) 34:3116–32. doi: 10.1002/sim.6546

26. Nelson KP, Zhou TJ, Edwards D. Measuring intrarater association between correlated ordinal ratings. *Biom J Biom Z.* (2020) 62:1687–701. doi: 10.1002/bimj.201900177

27. Giordana P, Baqué-Juston MC, Jeandel PY, Mondot L, Hirlemann J, Padovani B, et al. Contrast-enhanced ultrasound of carotid artery wall in takayasu disease: first evidence of application in diagnosis and monitoring of response to treatment. *Circulation.* (2011) 124:245–7. doi: 10.1161/CIRCULATIONAHA.110.006668

28. Lensen KDF, Comans EFI, Voskuyl AE, van der Laken CJ, Brouwer E, Zwijnenburg AT, et al. Large-vessel vasculitis: interobserver agreement and diagnostic accuracy of 18F-FDG-PET/CT. *BioMed Res Int.* (2015) 2015:914692. doi: 10.1155/2015/914692

29. Aschwanden M, Imfeld S, Staub D, Baldi T, Walker UA, Berger CT, et al. The ultrasound compression sign to diagnose temporal giant cell arteritis shows an excellent interobserver agreement. *Clin Exp Rheumatol.* (2015) 33:S113–115.

30. Schäfer VS, Chrysidis S, Schmidt WA, Duftner C, Iagnocco A, Bruyn GA, et al. OMERACT definition and reliability assessment of chronic ultrasound lesions of the axillary artery in giant cell arteritis. *Semin Arthritis Rheum.* (2021) 51:951–6. doi: 10.1016/j.semarthrit.2021.04.014

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EDITED BY
Stavros Chrysidis,
Sydvestjysk Sygehus, Denmark

REVIEWED BY
Hubert De Boysson,
Centre Hospitalier Universitaire de Caen, France
Johannes Fessler,
Medical University of Graz, Austria

*CORRESPONDENCE
Pavlos Stamatis
pavlos.stamatis@med.lu.se

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Pathogenesis of giant cell arteritis with focus on cellular populations

Pavlos Stamatis[1,2]*, Carl Turesson[3], Despina Michailidou[4] and Aladdin J. Mohammad[1,5]

[1]Rheumatology, Department of Clinical Sciences, Lund University, Lund, Sweden, [2]Rheumatology, Sunderby Hospital, Luleå, Sweden, [3]Rheumatology, Department of Clinical Sciences Malmö, Lund University, Malmö, Sweden, [4]Division of Rheumatology, Department of Medicine, University of Washington, Seattle, WA, United States, [5]Department of Medicine, University of Cambridge, Cambridge, United Kingdom

Giant cell arteritis (GCA), the most common non-infectious vasculitis, mainly affects elderly individuals. The disease usually affects the aorta and its main supra-aortic branches causing both general symptoms of inflammation and specific ischemic symptoms because of the limited blood flow due to arterial structural changes in the inflamed arteries. The pathogenesis of the GCA is complex and includes a dysregulated immune response that affects both the innate and the adaptive immunity. During the last two decades several studies have investigated interactions among antigen-presenting cells and lymphocytes, which contribute to the formation of the inflammatory infiltrate in the affected arteries. Toll-like receptor signaling and interactions through the VEGF-Notch-Jagged1 pathway are emerging as crucial events of the aberrant inflammatory response, facilitating among others the migration of inflammatory cells to the inflamed arteries and their interactions with the local stromal milieu. The increased use of checkpoint inhibitors in cancer immunotherapy and their immune-related adverse events has fed interest in the role of checkpoint dysfunction in GCA, and recent studies suggest a dysregulated check point system which is unable to suppress the inflammation in the previously immune-privileged arteries, leading to vasculitis. The role of B-cells is currently reevaluated because of new reports of considerable numbers of plasma cells in inflamed arteries as well as the formation of artery tertiary lymphoid organs. There is emerging evidence on previously less studied cell populations, such as the neutrophils, CD8+ T-cells, T regulatory cells and tissue residing memory cells as well as for stromal cells which were previously considered as innocent bystanders. The aim of this review is to summarize the evidence in the literature regarding the cell populations involved in the pathogenesis of GCA and especially in the context of an aged, immune system.

KEYWORDS

vasculitis pathogenesis, giant cell arteritis, innate immunity, adaptive immunity, cytokine signatures, check-point dysregulation

Introduction

Giant cell arteritis (GCA) is a non-infectious vasculitis affecting medium and large size arteries, especially the aorta and its main branches (1). It is the most common vasculitis in the western world with an incidence ranging from 5.8 to 22.2 per 100 000 inhabitants aged ≥50 years (2–5). Epidemiologic studies in the northern hemisphere have shown a clear north-to-south and west-to-east gradient, with the disease affecting mostly Caucasians (2, 3, 5–7). In Europe and North America, the female to male ratio is nearly 3:1 whereas the ratio tends to be 1:1 in western Asia (6, 8). The mean age at the diagnosis is 75 years (2, 3). Headache, scalp tenderness, jaw claudication, visual symptoms, polymyalgia rheumatica and arm claudication are common symptoms of the disease. Visual loss, stroke and aortic aneurysms are among the most feared manifestations of the disease. Most patients develop concurrently constitutional symptoms as malaise, fever, anorexia and weight loss as a consequence of the uncontrolled inflammation (9, 10). Elevated inflammatory markers are present in the majority of the patients (11, 12). In the appropriate clinical context, a positive temporal artery biopsy or typical imaging findings are required for the diagnosis of GCA. Glucocorticoids (GCs) are the mainstay of the treatment and other immunosuppressive agents are administrated adjunctively to reduce the exposure to GCs (13, 14).

GCA is traditionally considered to be an immune-mediated disease where the responsible vasculitogenic antigen(s) has yet not been identified. Overexpression of MHC class II genes located in the regions between HLA-DRA and HLA-DRB1 and even the over-presentation of genes located in the HLA-DQA1 and HLA-DQA2 suggest that GCA is an antigen driven immune mediated disease (15–17). Additionally, the presence of clonally expanded T-cells in different arterial sites suggests that there is a particular response to specific epitopes (15, 18, 19).

The arterial mural layers are considered the primary fields where the events of the inflammatory cascade take place. In GCA, large and medium sized arteries with diameter ≥2,000 μm are usually affected (20). These arteries have 3 mural layers: the intima, the media, and the adventitia. The arterial wall contains endothelial cells, vascular smooth cells, elastic membranes, matrix and fibroblasts (20). In these large arteries, the necessary nutrients cannot reach all the mural layers by diffusion from the lumen, and especially the high energy-demanding media layer. A microvasculature system is necessary, to transfer all the necessary nutrients from the arterial lumen to all 3 arterial layers. This microvasculature system is also called vasa vasorum ("vessels of the vessel"). In contrast with small arteries which do not have vasa vasorum, there are resident vascular dendritic cells (vasDCs) in the interface between the media and the adventitia of large arteries (15, 20). These cells play a critical role in the pathogenesis of GCA, which involves both the innate and the adaptive immune system.

Innate immune system in GCA

Toll-like receptors

The Toll-like receptors (TLR) are a family of transmembrane proteins which were identified in the mid 1990's. So far 10 types of TLRs have been identified. The TLRs 1, 2, 4, 5, 6 and 10 are expressed on the cellular surface and the TLRs 3, 7, 8 and 9 are expressed in cytosolic vesicles (21). TLRs act as pattern recognition receptors (PRRs), binding pathogen-associated molecular pattern ligands (PAMPs) and damage-associated molecular pattern ligands (DAMPs) (21, 22). The PAMPs originate directly from microbial agents, whereas the DAMPs are damage products from the inflamed tissues which have been produced during the "battle" between the host's immune system and the invader (21–23). In the event of a dysregulated interaction between the immune system and the specific tissue (20), DAMPs may act as kick-starters of an inflammatory response even in the absence of infection, trauma and ischemia (24). Several studies have pinpointed dendritic cells (DCs) as key players in this dysregulated interaction between the immune system and the arterial wall (19, 20, 25). Varying combinations and patterns of TLRs may expressed in the vasDCs of different arteries and an intriguing hypothesis could be that the activation of a specific TLR pattern leads to a specific immune response in arteries sharing the same or similar TLRs pattern, offering a possible explanation for the tissue tropism in GCA (20, 26).

Dendritic cells

DCs comprise an important link between the innate and adaptive immunity. Several studies have shown that this population of vasDCs, which is dysregulated in GCA, has a key role in the pathogenesis of the disease (19, 20). These vasDCs usually reside at the adventitia-media border and in normal arteries are tolerogenic which means that they don't have the ability to stimulate T-cells (19). A plausible hypothesis is that PAMPs and DAMPs from the main circulation (e.g., from one or more infectious agents in susceptible individuals) may reach the adventitia-media border *via* vasa vasorum (19, 26). In individuals predisposed for GCA (by TLR polymorphisms or other genetic and/or environmental factors), vasDCs may be activated by the presence of these danger signals, gaining T stimulatory capacity (15, 19, 26, 27). This activation causes the migration of these DCs into the media, where DCs produce chemotactic factors (e.g., CCL19 and CCL21) which in turn cause the migration and activation of T-cells and macrophages (19, 20). The subsequent inflammatory cascade, orchestrated mainly by Th1- and Th17-cell mediated responses, contributes to the granulomatous infiltrate seen in GCA (20, 28).

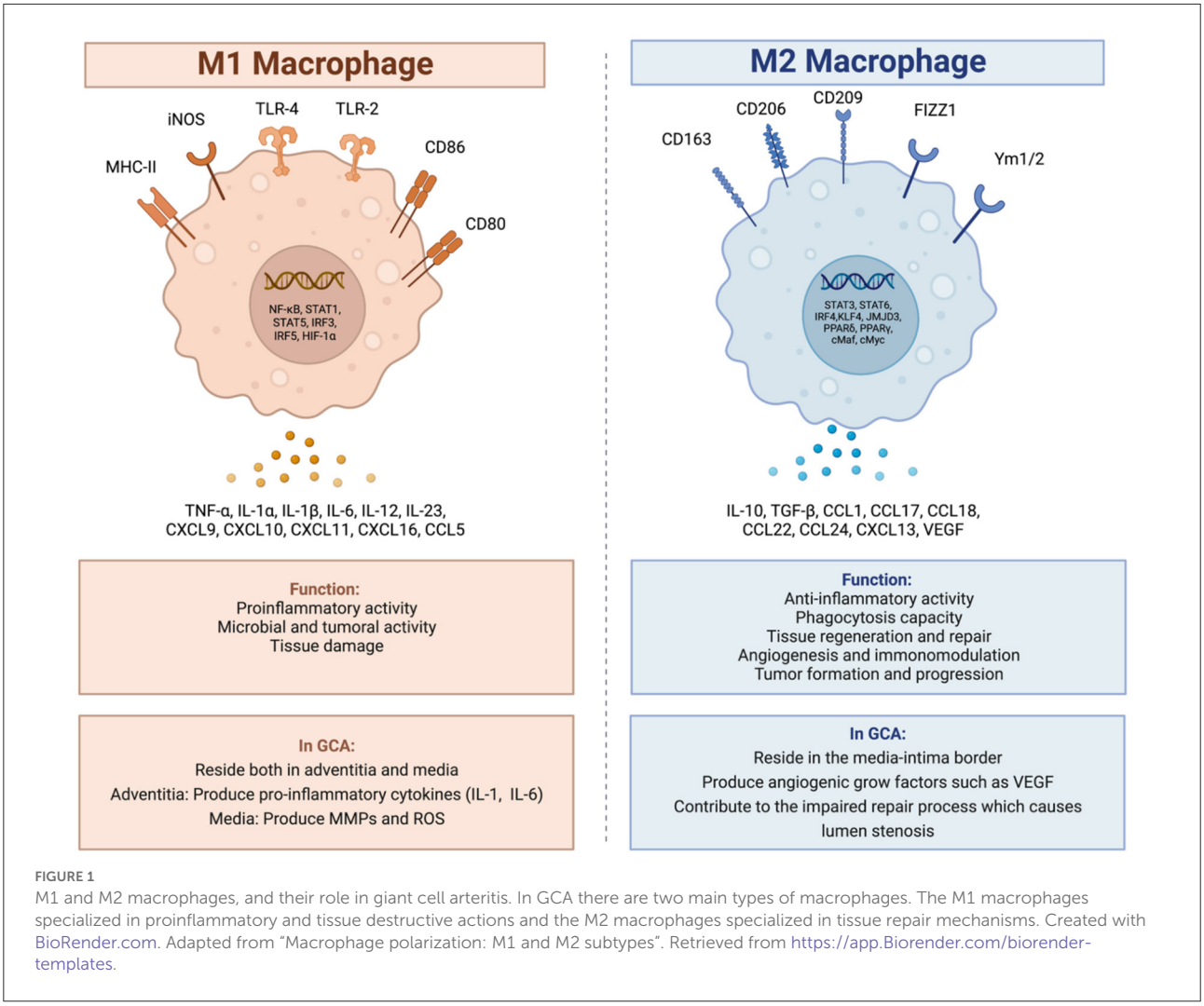

FIGURE 1
M1 and M2 macrophages, and their role in giant cell arteritis. In GCA there are two main types of macrophages. The M1 macrophages specialized in proinflammatory and tissue destructive actions and the M2 macrophages specialized in tissue repair mechanisms. Created with BioRender.com. Adapted from "Macrophage polarization: M1 and M2 subtypes". Retrieved from https://app.Biorender.com/biorender-templates.

Macrophages

The wall of normal medium-sized and large arteries is usually devoid of macrophages and T-cells (64). The macrophages are recruited to the arterial layers probably by activated vasDCs and T cells *via* vasa vasorum (15). Chemokine release from vascular smooth muscle cells (VSMCs), induced by IFN-γ, has been shown to be important for this recruitment (29). Recently, Watanabe et al. showed that monocytes from patients with GCA produce high amounts of matrix metalloproteinase 9 (MMP-9), which allows them to digest the basement membrane of vasa vasorum capillaries and enter the adventitial tissue, and thus exerting tissue-invading abilities and at the same time facilitating the invasion of other inflammatory cell populations (30).

Among these macrophages, there are two main types, polarized in response to the microenvironment of the arterial wall: the M1 phenotype and the M2 phenotype (Figure 1) (15, 31). The M1 macrophages are specialized in proinflammatory actions whereas the M2 macrophages are more specialized in tissue-repairing mechanisms (20).

In GCA, activated M1 macrophages reside both in the adventitia and in the media. In the adventitia, the macrophages produce pro-inflammatory cytokines such as IL-1 and IL-6 contributing to the maintenance of the inflammatory response (15, 18, 31), whereas in the media, the M1 activated macrophages, produce molecules which contribute to the degradation of the arterial wall, molecules such as MMPs and reactive oxygen species (ROS) (15, 20, 32, 33).

The M2 activated macrophages reside at the media-intima border producing angiogenic growth factors such as vascular endothelial growth factor (VEGF) contributing to the morphological and structural changes of the arterial lumen with

wall-thickening and stenosis as a part of a dysregulated repair process (15, 18).

The typical granulomas in GCA consist of activated T-cells, macrophages and histiocytes, usually including multinucleated giant cells (20). Multinucleated giant cells are the histopathological hallmark of giant cell arteritis found in up to 75% of the positive temporal biopsies (34–36). They are the result of fusion of activated macrophages (37). This process, and the differentiation of macrophages to effector cells in the vasculitis lesions, have been shown to be partly driven by granulocyte-macrophage colony stimulating factor (GM-CSF) and macrophage stimulating factor (M-CSF) signaling (38).

Neutrophils

Neutrophils are crucial mediators of the innate immune response (39) and play a vital role in the pathogenesis of many autoimmune diseases *via* release of neutrophil extracellular traps (NETs) (40). Circulating immature neutrophils were recently identified in patients with GCA that extravasated into the surrounding tissues of temporal arteries and produced elevated levels of extracellular ROS leading to enhanced vascular damage (41). Some other studies have demonstrated enhanced neutrophil activation as assessed by elevated levels of N-formyl methionine (fMET) that is a potent neutrophil chemoattractant, and calprotectin in the peripheral blood of patients with GCA. Circulating fMET was capable for mounting a de novo neutrophil activation *in vitro*, in a formyl peptide receptor 1 (FPR1)-dependent manner (42, 43). Neutrophilic infiltration has also been observed at the adventitia and media of involved arteries in GCA (44, 45) with presence of NETs identified in temporal artery biopsies from patients with GCA (46).

Adaptive immune system in GCA

T-cells

In a manner similar to the macrophages, the medium-sized and large arteries are normally devoid of T-cells (20). In GCA, activated vasDCs, residing in the adventitia-media border near the vasa vasorum, secret chemotactic factors which attract T-cells to these arteries. Consequently, depending on the interaction between the antigen-presenting cells and T-cells, T-cells differentiate into two main T-helper (Th) lineages: the Th17 and the Th1 lineage (Figure 2) (20).

Th17 cells

The Th17 cells constitute a key T-cell population in the pathogenesis of GCA. The frequencies of Th17 cells in the peripheral blood measured by flow cytometry have been consistently reported to be higher in patients with GCA in comparison to healthy controls (28, 47, 48). Naïve T-cells, under the stimulation of TGF-β and IL-6 or IL-21 upregulate the IL-1R and IL-23R (20). Consequently, the presence of TGF-β, IL-1β, IL-6 and IL-21 leads to the differentiation of naïve T-cells toward to the Th17 lineage (Figure 2) (49). The activated Th17 cells produce a plethora of cytokines such as IL-17, 1L-21, IL-22 and chemokine ligand 20 (CCL20) (20, 49). The production of these cytokines and chemokines contributes directly and indirectly both to the systemic manifestations of the disease and to the local arterial damage (e.g., the stimulating effect of IL-17 to macrophages). However, after treatment with GCs, both the number of Th17 cells and the concentration of Th17-related cytokines are markedly reduced in patients with GCA, both locally and in the peripheral blood of the patients (20, 28).

Th1 cells

The Th1 cells is another sub-population of T-cells which is critically involved in the pathogenesis of GCA. Unlike Th17 cells, the number of Th1 cells and the Th1-related cytokines seem not to be affected by the treatment with GCs, as they remain elevated both in the arterial tissue and in the blood (28). The presence of IL-12 in the arterial microenvironment shifts the differentiation of naïve T-cells toward to the Th1 lineage leading to the production of the powerful inflammatory cytokine IFN-γ (Figure 2) (20, 50). IL-12 has a key role in the activation of macrophages, the production of damage molecules (MMPs, ROS etc.) and the proliferation and migration of vascular smooth muscle cells (20).

T-regulatory cells

Abnormalities of T-regulatory cells (T-regs) also contribute to the pathogenesis of GCA. The high concentrations of IL-6, IL-21 and IL-23 in the microenvironment cause the blockage of the Forkhead box protein P3 (FOXP3), a transcriptional factor which is necessary for the differentiation of T-regs (Figure 2). Additionally, the presence of these cytokines, upregulates the transcriptional factor RORγt which stimulates the Th17 differentiation (51, 52). Consequently, the frequencies of T-regs in patients with GCA measured by flow cytometry have been reported low (47, 48). Recently, a pathogenic role of Tregs has also been proposed. Miyabe et al., demonstrated a pathogenic T-reg phenotype with impaired suppressor capacity and increased IL-17 production (53). Thus, in patients with GCA the Tregs are not only decreased in number, but their functionality is also impaired.

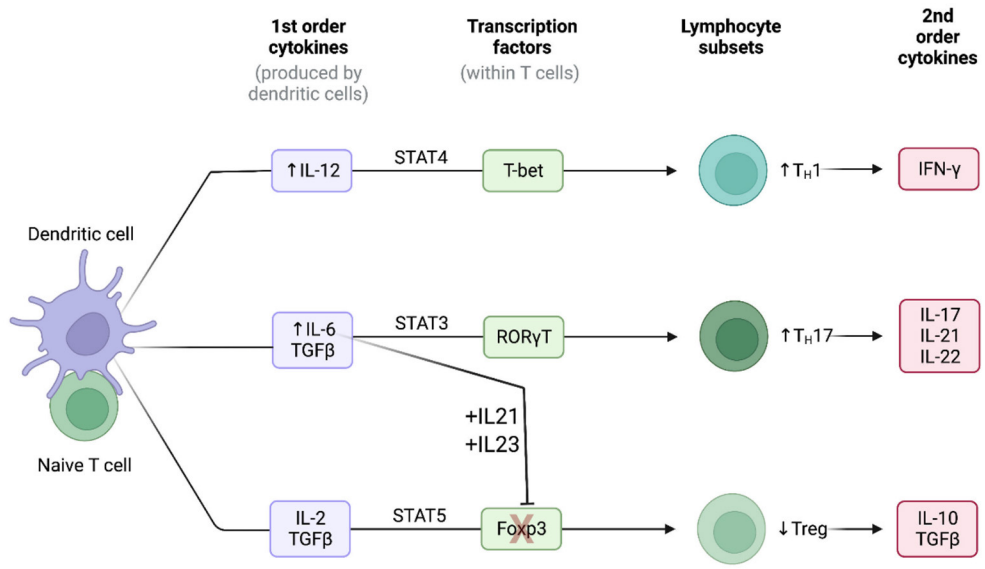

FIGURE 2
Cytokine signatures in GCA. Lineage polarization of naive T-cells in giant cell arteritis. Created with BioRender.com. Adapted from "Induction of 2nd order cytokines". Retrieved from https://app.Biorender.com/biorender-templates.

CD8+ T cells

The relative low numbers of CD8+ T cells both in the peripheral blood and in affected arteries has initially implicated a limited role of CD8+ T cells in the pathogenesis of GCA (54–56). However, a defect in peripheral immunosuppressive CD8+ Tregs have been recently demonstrated in the elderly (56, 57). CD8+ T regs normally regulate the activation and proliferative expansion of CD4+ T cells. Furthermore, it is now known that CD8+ T cells are more susceptible to age-related changes and their number decrease with increased age whereas naïve CD4+ cell are more resistant to age-related changes (58, 59). Thus, CD8+ T cells may have an unexplored contribution to the induction of the disease although they are not present in great number in the inflammatory infiltrate (60).

Tissue-resident memory cells

Tissue-resident memory T-cells (a subset of memory T-cells) appears to play a critical role in sustaining the inflammatory process. These cells stay on local tissues instead of returning to secondary lymphoid organs (61). The reason for this is to provide a rapid and effective response upon antigen re-encountering in the tissue. In GCA, it is now believed that these cells play a crucial role in the renewal and maintenance of the inflammatory infiltrate (62, 63).

B-cells

The role of B cells in GCA is not currently understood. It is believed that the B cells do not exert a key role in the pathogenesis of GCA. Previous theories regarding specific autoantibodies (e.g., cardiolipin antibodies) which could have a role in the pathogenesis of GCA have not confirmed by other studies (64–66). However, a recent study which investigated the changes in the histopathological image between the initial biopsy and a second follow up biopsy, randomly performed 3, 6, 9 or 12 months after the initial biopsy, showed the presence of plasma cells in the inflammatory bulk. In the initial biopsies, plasma cells were recorded in the 83% of the TABs whereas the percentage was lower (40%) in the second follow up biopsy (67). In line with these observations, Ciccia et al. (25) demonstrated that in patients with GCA, and more specific in the media layer of the temporal artery, there is a unencapsulated formation consisted of B cell aggregates, follicular dendritic cells, surrounding T cells and high endothelial venules. These structures are called as artery tertiary lymphoid organs (ATLOs). The ATLOs are formed postnatally and in response to chronic inflammation. Newly formed lymphatic vessels may transfer cytokines, chemokines, antigens, PAMPs and DAMPs from the arterial microenvironment to ATLOs. ATLOs were absent in healthy controls and were present in patients with GCA independently of the presence of atherosclerosis (25, 68). Interestingly, B cell survival factors such as BAFF and APRIL were present at higher levels in patients with GCA than in healthy controls (25). These factors are produced by endothelial cells and vascular smooth muscle cells, indicating an interaction

between stromal cells and immune cells (25). Recently, a study from Netherlands, following a previous study from the same group which showed low circulating B-cells in active GCA, demonstrated massive and organized B-cell infiltrates in the aorta of patients with LV-GCA (69, 70).

Figure 3 illustrates important steps in the GCA pathogenesis.

Cytokine signatures in GCA

The IL-6–IL-17 signature

IL-6 is a pleiotropic cytokine which can be secreted both from immune and stromal cells (endothelial cells, fibroblasts, and vascular smooth muscle cells), and is therefore an important mediator in the crosstalk between the immune system and the injured tissue (20, 71). IL-6 contributes to elevation of inflammatory markers through the activation of hepatocytes and plays an important role in the differentiation of naïve T-cells into functional lineages. More specifically, IL-6 in the presence of TGF-β steers the T cell differentiation toward the Th-17 lineage and at the same time, in synergy with IL-21 and IL-23, blocks the transcription factor FOXP3 which is essential for the differentiation of Tregs (Figure 2) (20, 71, 72). Thus, the presence of IL-6 exerts proinflammatory effects by differentiating naïve T-cells into the inflammatory Th-17 subset and restricts possible counteractions of the immune system by reducing (in absolute number and/or functionality) anti-inflammatory T-cells as T-regs (20).

The Th-17 cells produce a plethora of proinflammatory cytokines such as IL-8, IL-17, IL-21, IL-22, IL-26, CCL 20 and GM-GSF (20). The receptors of these cytokines are located both locally (e.g., IL-17 dependent activation of macrophages, endothelial cells, vascular smooth muscle cells and fibroblasts) and remotely (e.g., IL-22 mediated hepatocyte activation and production of acute phase reactants) (20, 73, 74). At early disease stages, a combination of Th-17 related cytokines is found both in the inflammatory infiltrate and in the peripheral blood. However, a previous study has demonstrated that treatment with GCs is highly effective in downregulating the Th-17-axis, by rapidly suppressing the production of IL-1, IL-6, and IL-23 cytokines, cytokines which are essential for the differentiation of Th17 cells (28). Consequently, the production of IL-17 is suppressed both in blood and in the inflamed arteries.

The IL-12–IFN-γ signature

In GCA-affected arteries, activated vasDCs may be a source of IL-12 (20, 75). Following stimulation with IL-12, naïve CD4+ T cells undergo lineage polarization into Th1 cells, through activation of the master transcription factor T-bet and suppression of the master transcription factor GATA-3 which favors a Th2 lineage polarization (Figure 2) (72). Consequently, Th1 lineage-specific genes are expressed and Th2-related genes are suppressed. Activated Th1 cells secrete the powerful proinflammatory cytokine IFN-γ. Generally, IFN-γ is mainly produced by NK-cells, CD8+ T cells, Th1 cells, macrophages and DCs (76), and IFN-γ receptors are mostly encountered in granulocytes, monocytes and macrophages (56). IFN-γ not only enhances the ongoing inflammatory process but also intensifies the tissue injury (20). Furthermore, IFN-γ interacts with tissue stromal cells like VSMC and endothelial cells. VSMC under the influence of IFN-γ become either apoptotic or migratory, with direction toward intima, contributing to arterial luminal stenosis (20, 77). Contrary to the response of the Th-17 axis to GCs, Th-1 responses are regulated mostly by the IL-12–IFN-γ cytokines, and are therefore unaffected by standard immunosuppressive treatment, as demonstrated by studies of tissue transcripts and plasma concentrations of IFN-γ (20, 28).

It has recently been demonstrated that plasma levels of IFN-γ and other proteins related to T cell function may be elevated years before clinical disease onset (78), further underlining the importance of this pathway and suggesting that it may drive very early disease mechanisms.

Check point dysregulation in GCA

A second co-stimulatory signal (e.g., CD28/CD80-86) is required for the activation of T-cell dependent immunity when an antigen binds to a T-cell receptor (TCR) (79). This is balanced by inhibitory signals which limit T-cell activation (e.g., CTLA-4/CD80-86 and PD-1/PD-L1) (79). Malignant cells usurp the PD-1-PD-L1 pathway by expressing the immunoinhibitory ligand PD-L1. Consequently, these cancer cells deliver immunoinhibitory signals when they encounter PD-1+ T-cells and thus evade immunosurveillance (80). Therefore, the PD-1/PD-L1 checkpoint inhibition is a well-recognized target in cancer immunotherapy, providing revolutionary results by unleashing the force of T-cell-dependent immunity upon malignant cells. Interestingly, immune-related adverse events (irAEs), as the price of the uncontrolled T-cell activation, are frequent side effects of cancer immunotherapy evolving any organ or system (81). Among other irAEs, several case reports of patients developing GCA under treatment with PD-1/PD-L1 inhibitors (Nivolumab, Pembrolizumab) have been published recently (82–85). Indeed, in GCA it seems that there is a dysregulation in PD-1/PD-L1 checkpoint inhibition (86). PD-L1 is normally expressed in antigen-presenting cells, stromal cells, and tumor cells whereas PD1 is expressed in T-cells, B-cells, NK-cells, activated monocytes, and dendritic cells (80, 86). In

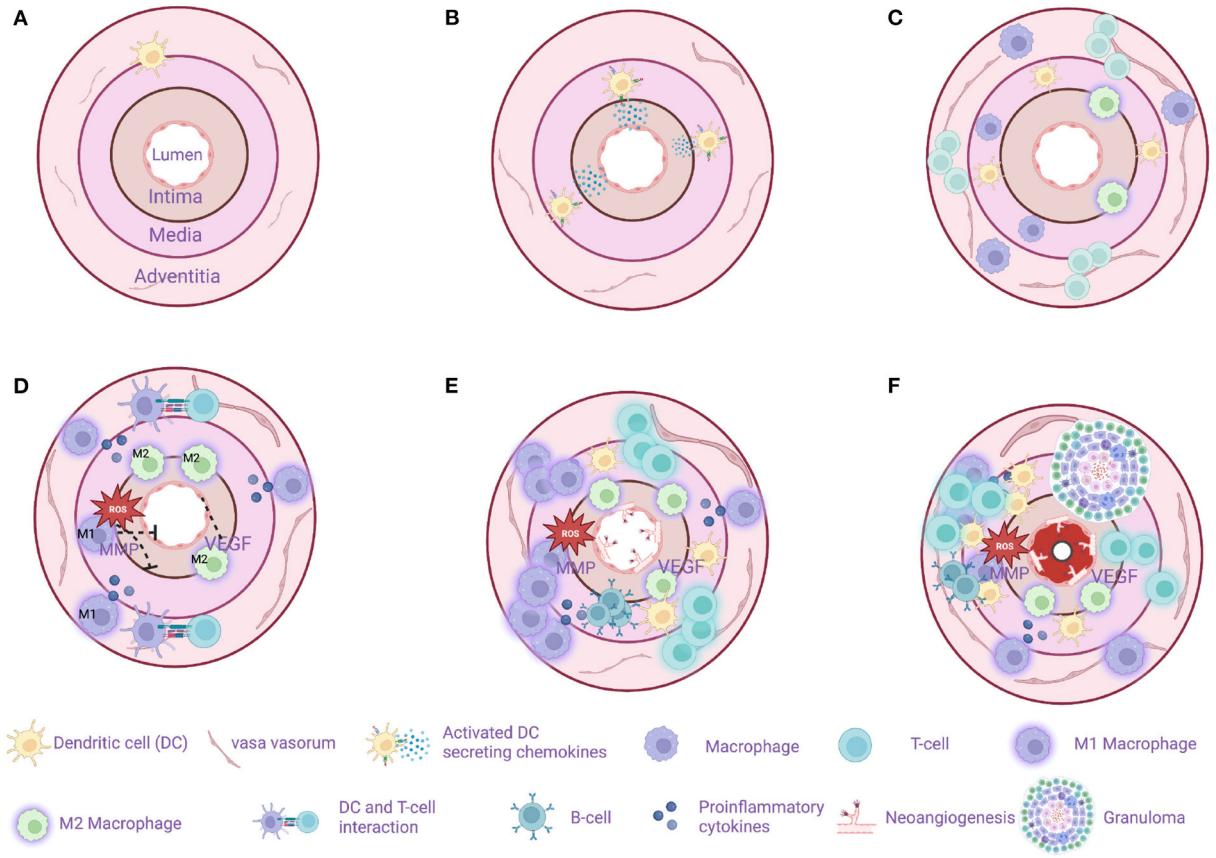

FIGURE 3
Model of sequential steps in pathogenesis of giant cell arteritis. **(A)** A healthy temporal artery is devoid of macrophages and T-cells. Vascular dendritic cells (vasDCs) are located in the adventitia-media border as a part of the immunosurveillance system. **(B)** The immunotolerance in GCA breaks and the activated vasDCs migrate to the media where they produce chemotactic factors. **(C)** Macrophages and T-cells are recruited from the main circulation probably entering the artery through the vasa vasorum. MMP-9 producing monocytes as well as the VEGF-NOTCH1-Jagged1 pathway facilitate the migration of macrophages and T-cells. **(D)** M1 macrophages located in the adventitia produce proinflammatory cytokines maintaining the inflammatory response. M1 macrophages located in the media produce tissue destructive molecules such as MMP-9 and reactive oxygen species (ROS). M2 macrophages in the intima-media border produce angiogenic growth factors such as VEGF contributing to the dysregulated repair mechanism in GCA. T cells continue to infiltrate the artery's layers with direction from adventitia to intima. **(E)** The destruction of the artery's tissue continues, T-cell inhibitory signals as the PDL1-PD1 are weakened in GCA leaving the activation of T-cell unopposed. At the same time a dysregulated repair process is in progress with excessive neo-angiogenesis and fibrosis. In some cases, artery tertiary lymphoid organs are located in the media. **(F)** The final result of the chronic inflammation is the formation of granulomas (up to 75% of the examined temporal artery biopsies) and the progressive stenosis and in some cases occlusion of the artery due to a maladaptive response to injury. Created with BioRender.com.

GCA-affected arteries, there is low expression of PD-L1 transcripts with no demonstrable expression of PD-L1 in vasDCs whereas most T-cells in the granulomas were PD-1 positive (87). Therefore, a mechanism which could inhibit excessive immunity in the arteries is defective, allowing infiltrating T-cells to remain activated. Of note, in healthy arteries, there was a high expression of PD-L1 transcripts and no expression of PD-1 transcripts, a finding confirming that normal arteries are devoid of T-cells (Figure 4) (88). Furthermore, *in vivo* blocking of PD1 in an animal model of GCA [chimeras of severe combined immunodeficiency (SCID) mice with transplanted human arteries, reconstituted with peripheral blood mononuclear cells from patients with GCA], exacerbated vascular inflammation and amplified T cell cytokine production (87).

It has been suggested that expression of PD-L1, and hence the PD-L1/PD-1 regulatory pathway, is regulated by glucose metabolites (89). The positive association between mitochondrial pyruvate levels and macrophage PD-L1 expression (89) and the reduced prevalence of diabetes mellitus at GCA diagnosis (90) are compatible with a protective effect of hyperglycaemia from such dysregulation. Recently, lower fasting blood glucose levels were demonstrated in individuals subsequently diagnosed with GCA, suggesting that metabolic factors influence the risk of GCA, possibly through effects on checkpoint function (91).

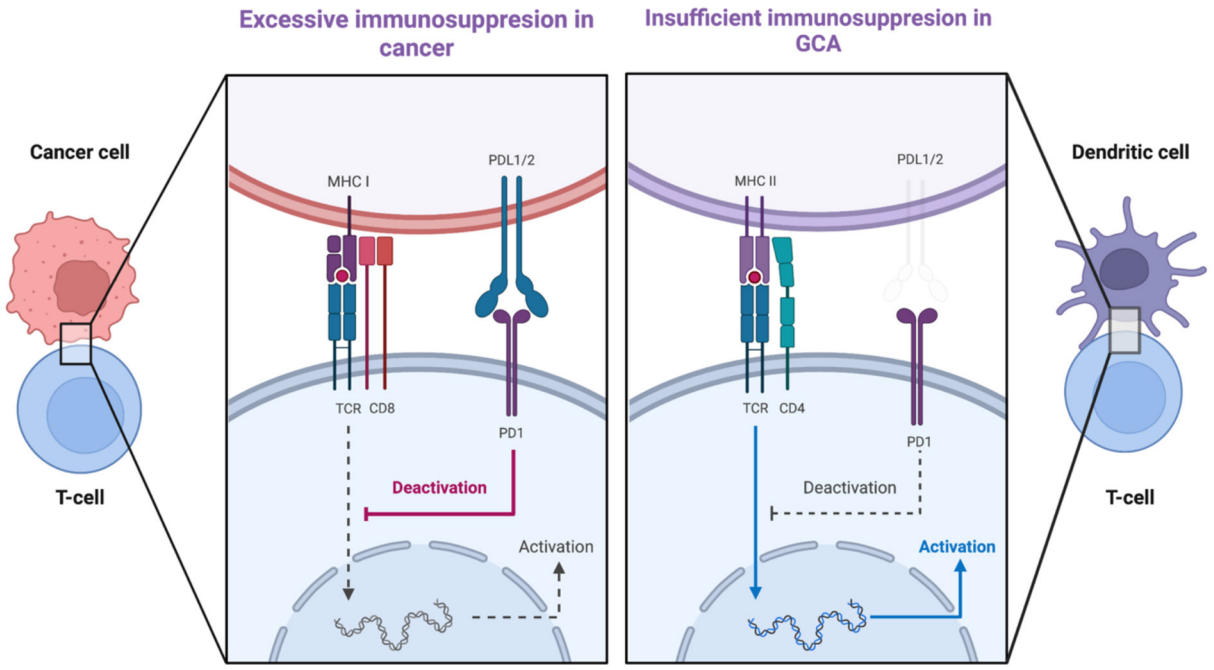

FIGURE 4
PDL1-PD1 checkpoint dysregulation in cancer and in giant cell arteritis. The expression of PDL1 on cancer cells delivers immunoinhibitory signals to T-cells and thus cancer cells evade tumor surveillance. In GCA, there is low expression of PDL1 on vascular dendritic cells whereas most T-cells arriving in the artery are PD1-positive. Created with BioRender.com. Adapted from "T-cell Deactivation vs. Activation." Retrieved from https://app.Biorender.com/biorender-templates.

Stromal interactions in GCA

The main components of the arterial vessel wall are the endothelial cells, vascular smooth muscle cells, vasDCs, elastic membranes, matrix, and fibroblasts. Theories which consider GCA as strictly an immune-mediated disease, where an unknown vasculitogenic stimulus breaks down the self-tolerance and elicits autoimmunity, overlook two major factors: (1) the age cut-off (2) the strict tissue tropism. Recent studies have tried to shed light on the interaction between the immune system and the local stromal milieu. The emerging theme is that stromal cells or extracellular matrix components could interact with the immune system playing a key role in breaking the self-tolerance and maintaining the inflammatory process.

Endothelial cells

Endothelial cells form a barrier between the circulating immune cells and the arterial wall. Endothelial cells have the capacity to interact with immune system by expressing various adhesion molecules, receptors, and ligands. Wen et al. demonstrated a model in which endothelial cells in vasa vasorum could induce pathogenic effector functions in CD4+ cells through VEGF-NOTCH1-Jagged1 interactions (57). An increased concentration of VEGF in the serum of patients with GCA have been demonstrated, which in turn, causes up-regulation of the Jagged1 ligand in endothelial cells of vasa vasorum (92, 93). The origin of the increased VEGF is currently unknown. Previous studies have also demonstrated that NOTCH1 is also aberrantly expressed in CD4+ cells of patients with GCA. Thus, the VEGF-NOTCH1-Jagged1 pathway facilitates the invasion of CD4+NOTCH1+ T cells into vessel wall and the polarization into Th1 and Th17 effector subsets (94, 95). Notably, a prerequisite for the invasion of T-cells in the arterial wall is that MMP-9 producing monocytes have first digested the basement membrane in order to open a way for the infiltrating T-cells (30, 63).

Vascular smooth muscle cells

Layers of VSMC are located in the media layer of medium- and large-sized arteries. These cells express in their surface molecules which allows them to communicate with neighboring cells, e.g., NOTCH1receptors and their Jagged1 and Delta1 ligands (20). Thus, as they act as signal-transducing and signal-receiving cells, they can influence the tissue microenvironment and the communication with the immune cells which bear the same receptors and ligands (20). Furthermore, upon proper

stimulation, they proliferate and migrate to the intima where they produce abnormal matrix proteins and contribute to narrowing and potentially occlusion of the lumen. In the model with implanted human arteries in SCID mice, blockade of the NOTCH signaling pathway markedly reduced the transformation of VSMC from a contractile to non-contractile phenotype in arteries with established GCA. Furthermore, the T-cell density in the infiltrate was reduced and likewise the production of IFN-γ and IL-17 (95).

Another elegant study has recently demonstrated increased concentration of endothelin 1 (ET-1) in GCA-affected arteries (96). The main source of ET1 was leukocytes and monocytes and both ET receptors were upregulated in infiltrating leukocytes, endothelial cells and VSMC. Thus, this enabled the interaction between stromal cells and infiltrating immune cells. The ET-1 mediated activation of VSMC promoted their migration from media to intima with concurrent production of MMP-2 which facilitated the fragmentation of the internal elastic lamina. The authors concluded that, beyond vascular tone regulation, the ET-1 mediated activation of VSMC plays an important role in vascular remodeling in GCA (96).

Extracellular matrix

Aging causes changes in the structure of arterial walls. The walls of the arteries become thicker and stiffer. They also lose their elasticity and therefore are more prone to age-related comorbidities, such as hypertension (97). These structural changes also reflect changes in the composition of extracellular matrix, e.g., less elastin more collagen (97). Little is known about the potential role of extracellular matrix's components on initiating or suppressing an autoimmune response. For instance, in multiple sclerosis, galectin 1A, an endogenous glycan binding protein which is produced by stromal cells and subsequently stored in extracellular matrix, found to elicit a tolerogenic response by inducing tolerogenic DCs which produce IL-27. These DCs blunt Th1 and Th17 responses and promote the differentiation of Tregs (98).

The role of immune aging and inflammaging

During the last decade a new research field has emerged, the field of geroscience, which investigates the link between aging and age-related chronic disease (99). Seven pillars of aging were identified: (i) adaptation to stress, (ii) epigenetics, (iii) inflammation, (iv) macromolecular damage, (v) metabolism, (vi) proteostasis, and (vii) stem cells and regeneration (99, 100). These pillars are interconnected, and interact with each other. It seems that abnormalities in each of these pillars cause inflammation which in turn affects all the other pillars, making inflammation the common denominator in the pathogenesis of age-related diseases (100). This chronic, low-grade, sterile inflammation, which increases with increasing age, is called inflammaging (100, 101).

The term immunosenescence describes all the age-related changes in the immune system (102). The main characteristics of immunosenescence are (1) the low-grade sterile inflammation (inflammaging), (2) the impaired wound healing, (3) the increased susceptibility to infections and cancer, (4) the lower responses to antigen stimulation (e.g. vaccinations) as well as, (5) the increased risk for autoimmune diseases (103). Both the innate and the adaptive immune system are affected by the process of aging (Figure 5). In the bone marrow, an important step toward immune aging is the myeloid skewing of hematopoietic stem cells (HSC) with decreased ability to differentiate into the lymphoid lineage (104). Changes in the microarchitecture of the spleen have also described in the elderly with increased atrophy (105). Thymus involution begins in early childhood and by the age of 75 year the thymus is mostly a fat tissue (105, 106). After the 5th decade of life and with further increased age, the number of circulating naïve T-cells, both CD8+ and CD4+ are markedly reduced although the reduction is less pronounced for the CD4+ populations (107, 108). With increasing age, there is reduced CD28 expression in both CD4+ and CD8+ lymphocytes (109–111). In individuals older than 65 years, CD4+CD28- cells represent up to 50% of the total CD4 lymphocytes whereas in young people the respective frequency ranges from 1 to 2.5% (109, 112). The reduced CD28 expression has been proposed both as a marker of normal aging and as a marker of early aging under chronic inflammatory stimulation (109, 111). Of note, these CD4+CD28- cells are potent secretors of pro-inflammatory cytokines such as IFN-γ and IL-2 (109, 113). Interestingly, increased numbers of CD4+CD28- cells have been reported both in peripheral blood and vascular lesions in patients with GCA (114). On the other hand, there is ample support for a role of CD28 co-stimulation in the pathogenesis of GCA (63), and treatment with CTLA4-Ig, which blocks CD28, has been shown to reduce the risk of relapse in patients with GCA (115). This apparent paradox may reflect co-stimulation in de novo activation of T cells that drives the disease process, leading to emergence of immunosenescent cells that retain some effector functions.

Furthermore, there is a gradual decline in the number of naïve T-cells in the periphery whereas the numbers of memory T-cells increase with age (105). The number of naïve B cells also declines with increased age as well as the quality of the humoral immune response characterized by lower antibody responses, decreased high-affinity antibodies and decreased IgG isotype class switching (105, 107, 116). The innate immune system is also profoundly affected by aging as there are several functional declines in the cellular populations comprising the innate immune system. With increasing age of the host, the granulocytes exhibit reduced functions including impaired

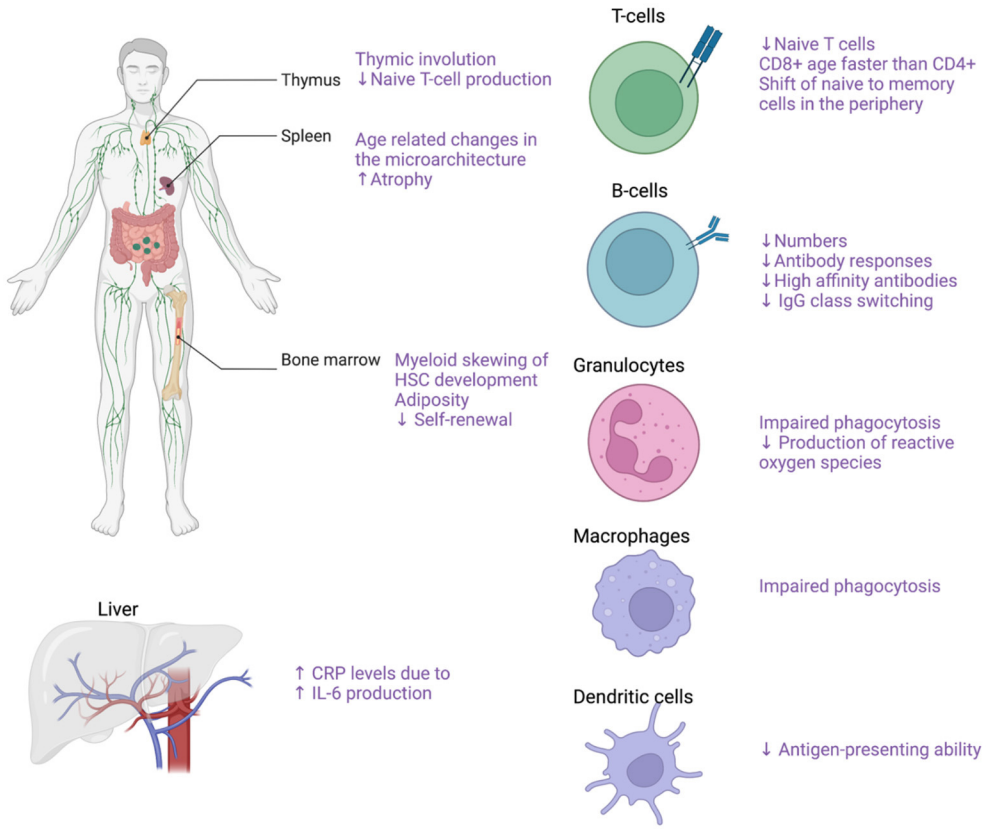

FIGURE 5
Effects of aging on the immune system. Effects of aging on the immune system with focus on the main cellular populations contributing to GCA pathogenesis. Created with BioRender.com.

phagocytosis and reduced production of reactive oxygen species (107, 117, 118). Macrophage phagocytosis and the ability of DCs to maturate and present antigen is also gradually impaired with aging (107). Of note, average levels of proinflammatory cytokines such as TNF-a and IL6 were reported to be increased in the elderly, leading to higher production of C-reactive protein by the liver (107, 119, 120).

The role of infections in GCA

Cyclical fluctuations in the incidence of GCA and the granulomatous nature of the infiltrate favor theories that infection may play a role in the pathogenesis of the disease (121, 122). Epidemiological studies have shown weak to moderate associations between infections and the subsequent development of GCA (123, 124). Several studies have reported associations between antecedent infections, both viral and bacterial, and the future development of GCA (122, 125–129). However, these results were not reproducible in other, independent studies. It is doubtful whether an infectious agent could influence the immune system so profoundly and on so many levels. A more plausible hypothesis could be that an infection is the last part of the drama, where the infection causes an unpredictable and strong reaction of the immune system, because of the cumulative effect of other previous dysregulated interactions between the immune system and host tissues. On the other hand, the demonstration of elevated plasma IFN-γ levels years before GCA onset suggest that host responses to a range of different microbial pathogens may be involved in early stages of the disease process (78).

Clinical implications

Insights on the role of cellular populations in the pathogenesis in GCA, and their variability, may help us to define clinically meaningful disease subsets. Systematic studies of tissue and blood samples may lead to identification of patients at increased risk of relapse or severe complications. Such investigations might also guide future targeted therapy.

Several targeted immunosuppressive drugs have been used as add-on to GCs, with the aim of reducing long term GC use and related toxicity (130). As expected based on the biology

of IL-6, and its role in GCA, IL-6 inhibition by the anti-IL-6 receptor antibody tocilizumab is effective in GCA that has been verified by biopsy or large vessel imaging, and enables rapid GC tapering with reduced risk of relapse (13). Tocilizumab works equally well in patients with a clinical presentation dominated by cranial symptoms, and those presenting mainly with signs and symptoms of polymyalgia rheumatica. However, relapses after discontinuation of anti-IL-6 therapy do occur (131), possibly reflecting persistence of Th1 cells in chronic vascular infiltrates.

Preliminary results from a phase II randomized clinical trial indicated clinical efficacy for the IL-17A inhibitor secukinumab in patients with GCA (132). Targeting IL-17 would also be expected to affect mainly the IL-6-IL-17 pathway, potentially with greater short term anti-inflammatory effects compared to the impact on chronic aspects of the disease. These hypotheses need to be investigated in extended clinical trials.

Other agents that have been tried in the treatment of GCA include anti-CSF2 therapy using mavrilimumab (133), which blocks GM-CSF signaling, and would be expected to have an impact on giant cell formation, and JAK-inhibition [e.g. baricitinib (134)], which has a broader effect on intracellular signaling and activation of T cells and other cell populations that makes it promising as a strategy for treating GCA.

Conclusions

GCA is characterized by an aberrant immune response involving both the innate and adaptive immunity. It is doubtful whether a single external culprit (e.g., an infectious agent) could provoke such an extensive and chronic inflammatory response. Furthermore, theories of a single external culprit fail to explain the strict tissue tropism and why GCA affects mainly the elderly. Future studies may elucidate the contribution of internal factors, such as age-related changes in cell turnover, metabolism and dealing with molecular debris, in combination with the aging immune system. Epidemiological studies have shown a lower incidence of certain types of cancer in patients with GCA after diagnosis (135, 136). The development of the disease in some susceptible individuals could therefore be an epiphenomenon of a superior tumor surveillance, as response to cancer treatment with check point inhibitors has been associated with autoimmune related adverse events, including GCA (137, 138). Innate check-point dysregulation contributing to GCA development may be influenced by metabolic factors (89). The importance of T-cell dysregulation has been further underlined by the recent demonstration of elevated T-cell related cytokines years before disease onset (78).

Author contributions

PS, CT, DM, and AJM wrote the manuscript. PS contributed the figures. The idea for this review was conceived by PS. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised International Chapel Hill consensus conference nomenclature of vasculitides. *Arthritis Rheum.* (2013) 65:1–11. doi: 10.1002/art.37715

2. Catanoso M, Macchioni P, Boiardi L, Muratore F, Restuccia G, Cavazza A, et al. Incidence, prevalence, and survival of biopsy-proven giant cell arteritis in northern italy during a 26-year period. *Arthritis Care Res (Hoboken).* (2017) 69:430–8. doi: 10.1002/acr.22942

3. Stamatis P, Turkiewicz A, Englund M, Turesson C, Mohammad AJ. Epidemiology of biopsy-confirmed giant cell arteritis in southern Sweden—an update on incidence and first prevalence estimate. *Rheumatology (Oxford, England).* (2021). doi: 10.1093/rheumatology/keab269

4. Therkildsen P, de Thurah A, Hansen IT, Nørgaard M, Nielsen BD, Hauge EM. Giant cell arteritis: a nationwide, population-based cohort study on incidence, diagnostic imaging, and glucocorticoid treatment. *Semin Arthritis Rheum.* (2021) 51:360–6. doi: 10.1016/j.semarthrit.2021.01.007

5. Sharma A, Mohammad A, Turesson C. Incidence and prevalence of giant cell arteritis and polymyalgia rheumatica: a systematic literature review. *Semin Arthritis Rheum.* (2020) 50:1040–8. doi: 10.1016/j.semarthrit.2020.07.005

6. Pamuk ON, Donmez S, Karahan B, Pamuk GE, Cakir N. Giant cell arteritis and polymyalgia rheumatica in northwestern Turkey: clinical features and epidemiological data. *Clin Exp Rheumatol.* (2009) 27:830–3.

7. Kobayashi S, Yano T, Matsumoto Y, Numano F, Nakajima N, Yasuda K, et al. Clinical and epidemiologic analysis of giant cell (temporal) arteritis from a nationwide survey in 1998 in Japan: the first government-supported nationwide survey. *Arthritis Rheum.* (2003) 49:594–8. doi: 10.1002/art.11195

8. Bas-Lando M, Breuer GS, Berkun Y, Mates M, Sonnenblick M, Nesher G. The incidence of giant cell arteritis in Jerusalem over a 25-year period: annual and seasonal fluctuations. *Clin Exp Rheumatol.* (2007) 25:S15-7.

9. Tuckwell K, Collinson N, Dimonaco S, Klearman M, Blockmans D, Brouwer E, et al. Newly diagnosed vs. relapsing giant cell arteritis:

Baseline data from the GiACTA trial. *Sem Arthritis Rheum.* (2017) 46:657–64. doi: 10.1016/j.semarthrit.2016.11.002

10. Gonzalez-Gay MA, Barros S, Lopez-Diaz MJ, Garcia-Porrua C, Sanchez-Andrade A, Llorca J. Giant cell arteritis: disease patterns of clinical presentation in a series of 240 patients. *Medicine.* (2005) 84:269–76. doi: 10.1097/01.md.0000180042.42156.d1

11. Parikh M, Miller NR, Lee AG, Savino PJ, Vacarezza MN, Cornblath W, et al. Prevalence of a normal C-reactive protein with an elevated erythrocyte sedimentation rate in biopsy-proven giant cell arteritis. *Ophthalmology.* (2006) 113:1842–5. doi: 10.1016/j.ophtha.2006.05.020

12. Kermani TA, Schmidt J, Crowson CS, Ytterberg SR, Hunder GG, Matteson EL, et al. Utility of erythrocyte sedimentation rate and C-reactive protein for the diagnosis of giant cell arteritis. *Semin Arthritis Rheum.* (2012) 41:866–71. doi: 10.1016/j.semarthrit.2011.10.005

13. 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) 377:317–28. doi: 10.1056/NEJMoa1613849

14. Mahr AD, Jover JA, Spiera RF, Hernandez-Garcia C, Fernandez-Gutierrez B, Lavalley MP, et al. Adjunctive methotrexate for treatment of giant cell arteritis: an individual patient data meta-analysis. *Arthritis Rheum.* (2007) 56:2789–97. doi: 10.1002/art.22754

15. Koster MJ, Warrington KJ. Giant cell arteritis: pathogenic mechanisms and new potential therapeutic targets. *BMC Rheumatol.* (2017) 1:2. doi: 10.1186/s41927-017-0004-5

16. Carmona FD, Mackie SL, Martín J-E, Taylor JC, Vaglio A, Eyre S, et al. A large-scale genetic analysis reveals a strong contribution of the HLA class II region to giant cell arteritis susceptibility. *Am J Hum Genet.* (2015) 96:565–80. doi: 10.1016/j.ajhg.2015.02.009

17. Carmona FD, Coit P, Saruhan-Direskeneli G, Hernandez-Rodriguez J, Cid MC, Solans R, et al. Analysis of the common genetic component of large-vessel vasculitides through a meta-Immunochip strategy. *Sci Rep.* (2017) 7:43953. doi: 10.1038/srep43953

18. Weyand CM, Liao YJ, Goronzy JJ. The immunopathology of giant cell arteritis: diagnostic and therapeutic implications. *J Neuro-Ophthalmol.* (2012) 32:259–65. doi: 10.1097/WNO.0b013e318268aa9b

19. Ma-Krupa W, Jeon M-S, Spoerl S, Tedder TF, Goronzy JJ, Weyand CM. Activation of arterial wall dendritic cells and breakdown of self-tolerance in giant cell arteritis. *J Exp Med.* (2004) 199:173–83. doi: 10.1084/jem.20030850

20. Weyand CM, Goronzy JJ. Immune mechanisms in medium and large-vessel vasculitis. *Nat Rev Rheumatol.* (2013) 9:731–40. doi: 10.1038/nrrheum.2013.161

21. Kawai T, Akira S. The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. *Nat Immunol.* (2010) 11:373–84. doi: 10.1038/ni.1863

22. O'Neill L, Molloy ES. The role of toll like receptors in giant cell arteritis. *Rheumatology (Oxford, England).* (2016) 55:1921–31. doi: 10.1093/rheumatology/kew001

23. Patel S. Danger-Associated Molecular Patterns (DAMPs): the derivatives and triggers of inflammation. *Curr Allergy Asthma Rep.* (2018) 18:63. doi: 10.1007/s11882-018-0817-3

24. Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, et al. Inflammatory responses and inflammation-associated diseases in organs. *Oncotarget.* (2017) 9:7204–18. doi: 10.18632/oncotarget.23208

25. Ciccia F, Rizzo A, Ferrante A, Guggino G, Croci S, Cavazza A, et al. New insights into the pathogenesis of giant cell arteritis. *Autoimmun Rev.* (2017) 16:675–83. doi: 10.1016/j.autrev.2017.05.004

26. Deng J, Ma-Krupa W, Gewirtz AT, Younge BR, Goronzy JJ, Weyand CM. Toll-like receptors 4 and 5 induce distinct types of vasculitis. *Circ Res.* (2009) 104:488–95. doi: 10.1161/CIRCRESAHA.108.185777

27. Song GG, Choi SJ Ji JD, Lee YH. Toll-like receptor polymorphisms and vasculitis susceptibility: meta-analysis and systematic review. *Mol Biol Rep.* (2013) 40:1315–23. doi: 10.1007/s11033-012-2175-x

28. Deng J, Younge BR, Olshen RA, Goronzy JJ, Weyand CM, Deng J, et al. Th17 and Th1 T-cell responses in giant cell arteritis. *Circulation.* (2010) 121:906–15. doi: 10.1161/CIRCULATIONAHA.109.872903

29. Corbera-Bellalta M, Planas-Rigol E, Lozano E, Terrades-García N, Alba MA, Prieto-González S, et al. Blocking interferon γ reduces expression of chemokines CXCL9, CXCL10 and CXCL11 and decreases macrophage infiltration in ex vivo cultured arteries from patients with giant cell arteritis. *Ann Rheum Dis.* (2016) 75:1177–86. doi: 10.1136/annrheumdis-2015-208371

30. Watanabe R, Maeda T, Zhang H, Berry GJ, Zeisbrich M, Brockett R, et al. MMP (Matrix Metalloprotease)-9-producing monocytes enable T cells to invade the vessel wall and cause vasculitis. *Circ Res.* (2018) 123:700–15. doi: 10.1161/CIRCRESAHA.118.313206

31. Wagner AD, Goronzy JJ, Weyand CM. Functional profile of tissue-infiltrating and circulating CD68+ cells in giant cell arteritis. Evidence for two components of the disease. *J Clin Invest.* (1994) 94:1134–40. doi: 10.1172/JCI117428

32. Rodriguez-Pla A, Bosch-Gil JA, Rossello-Urgell J, Huguet-Redecilla P, Stone JH, Vilardell-Tarres M. Metalloproteinase-2 and−9 in giant cell arteritis: involvement in vascular remodeling. *Circulation.* (2005) 112:264–9. doi: 10.1161/CIRCULATIONAHA.104.520114

33. Rittner HL, Kaiser M, Brack A, Szweda LI, Goronzy JJ, Weyand CM. Tissue-destructive macrophages in giant cell arteritis. *Circ Res.* (1999) 84:1050–8. doi: 10.1161/01.RES.84.9.1050

34. Cavazza A, Muratore F, Boiardi L, Restuccia G, Pipitone N, Pazzola G, et al. Inflamed temporal artery: histologic findings in 354 biopsies, with clinical correlations. *Am J Surg Pathol.* (2014) 38:1360–70. doi: 10.1097/PAS.0000000000000244

35. Armstrong AT, Tyler WB, Wood GC, Harrington TM. Clinical importance of the presence of giant cells in temporal arteritis. *J Clin Pathol.* (2008) 61:669. doi: 10.1136/jcp.2007.049049

36. Chatelain D, Duhaut P, Schmidt J, Loire R, Bosshard S, Guernou M, et al. Pathological features of temporal arteries in patients with giant cell arteritis presenting with permanent visual loss. *Ann Rheum Dis.* (2009) 68:84–8. doi: 10.1136/ard.2007.084947

37. Brodbeck WG, Anderson JM. Giant cell formation and function. *Curr Opin Hematol.* (2009) 16:53–7. doi: 10.1097/MOH.0b013e32831ac52e

38. Jiemy WF, van Sleen Y, van der Geest KS, Ten Berge HA, Abdulahad WH, Sandovici M, et al. Distinct macrophage phenotypes skewed by local granulocyte macrophage colony-stimulating factor (GM-CSF) and macrophage colony-stimulating factor (M-CSF) are associated with tissue destruction and intimal hyperplasia in giant cell arteritis. *Clin Transl Immunol.* (2020) 9:e1164. doi: 10.1002/cti2.1164

39. Nauseef WM, Borregaard N. Neutrophils at work. *Nat Immunol.* (2014) 15:602–11. doi: 10.1038/ni.2921

40. Grayson PC, Kaplan MJ. At the Bench: Neutrophil extracellular traps (NETs) highlight novel aspects of innate immune system involvement in autoimmune diseases. *J Leukoc Biol.* (2016) 99:253–64. doi: 10.1189/jlb.5BT0615-247R

41. Wang L, Ai Z, Khoyratty T, Zec K, Eames HL, van Grinsven E, et al. ROS-producing immature neutrophils in giant cell arteritis are linked to vascular pathologies. *JCI Insight*. (2020) 5:e139163. doi: 10.1172/jci.insight.139163

42. Michailidou D, Duvvuri B, Kuley R, Cuthbertson D, Grayson PC, Khalidi NA, et al. Neutrophil activation in patients with anti-neutrophil cytoplasmic autoantibody-associated vasculitis and large-vessel vasculitis. *Arthritis Res Ther.* (2022) 24:160. doi: 10.1186/s13075-022-02849-z

43. Tombetti E, Hysa E, Mason JC, Cimmino MA, Camellino D. Blood biomarkers for monitoring and prognosis of large vessel vasculitides. *Curr Rheumatol Rep.* (2021) 23:17. doi: 10.1007/s11926-021-00980-5

44. Nadkarni S, Dalli J, Hollywood J, Mason JC, Dasgupta B, Perretti M. Investigational analysis reveals a potential role for neutrophils in giant-cell arteritis disease progression. *Circ Res.* (2014) 114:242–8. doi: 10.1161/CIRCRESAHA.114.301374

45. Foell D, Hernández-Rodríguez J, Sánchez M, Vogl T, Cid MC, Roth J. Early recruitment of phagocytes contributes to the vascular inflammation of giant cell arteritis. *J Pathol.* (2004) 204:311–6. doi: 10.1002/path.1660

46. Palamidas DA, Argyropoulou OD, Georgantzoglou N, Karatza E, Xingi E, Kapsogeorgou EK, et al. Neutrophil extracellular traps in giant cell arteritis biopsies: presentation, localization and co-expression with inflammatory cytokines. *Rheumatology (Oxford, England).* (2022) 61:1639–44. doi: 10.1093/rheumatology/keab505

47. Samson M, Audia S, Fraszczak J, Trad M, Ornetti P, Lakomy D, et al. Th1 and Th17 lymphocytes expressing CD161 are implicated in giant cell arteritis and polymyalgia rheumatica pathogenesis. *Arth Rheum.* (2012) 64:3788–98. doi: 10.1002/art.34647

48. Terrier B, Geri G, Chaara W, Allenbach Y, Rosenzwajg M, Costedoat-Chalumeau N, et al. Interleukin-21 modulates Th1 and Th17 responses in giant cell arteritis. *Arthritis Rheum.* (2012) 64:2001–11. doi: 10.1002/art.34327

49. Maddur MS, Miossec P, Kaveri SV, Bayry J. Th17 cells: biology, pathogenesis of autoimmune and inflammatory diseases, and therapeutic strategies. *Am J Pathol.* (2012) 181:8–18. doi: 10.1016/j.ajpath.2012.03.044

50. Weyand CM, Younge BR, Goronzy JJ. IFN-γ and IL-17: the two faces of T-cell pathology in giant cell arteritis. *Curr Opin Rheumatol.* (2011) 23:43–9. doi: 10.1097/BOR.0b013e32833ee946

51. Kimura A, Kishimoto T. IL-6: regulator of Treg/Th17 balance. *Eur J Immunol.* (2010) 40:1830–5. doi: 10.1002/eji.201040391

52. Barbi J, Pardoll D, Pan F. Metabolic control of the Treg/Th17 axis. *Immunol Rev.* (2013) 252:52–77. doi: 10.1111/imr.12029

53. Miyabe C, Miyabe Y, Strle K, Kim ND, Stone JH, Luster AD, et al. An expanded population of pathogenic regulatory T cells in giant cell arteritis is abrogated by IL-6 blockade therapy. *Ann Rheum Dis.* (2017) 76:898–905. doi: 10.1136/annrheumdis-2016-210070

54. Elling P, Olsson A, Elling H. CD8+ T lymphocyte subset in giant cell arteritis and related disorders. *J Rheumatol.* (1990) 17:225–7.

55. Kurata A, Saito A, Hashimoto H, Fujita K, Ohno S-i, Kamma H, et al. Difference in immunohistochemical characteristics between Takayasu arteritis and giant cell arteritis: It may be better to distinguish them in the same age. *Modern Rheumatol.* (2019) 29:992–1001. doi: 10.1080/14397595.2019.1570999

56. Watanabe R, Berry GJ, Liang DH, Goronzy JJ, Weyand CM. Cellular signaling pathways in medium and large vessel vasculitis. *Front Immunol.* (2020) 11:587089. doi: 10.3389/fimmu.2020.587089

57. Wen Z, Shimojima Y, Shirai T, Li Y, Ju J, Yang Z, et al. NADPH oxidase deficiency underlies dysfunction of aged CD8+ Tregs. *J Clin Invest.* (2016) 126:1953–67. doi: 10.1172/JCI84181

58. Moskowitz DM, Zhang DW, Hu B, Le Saux S, Yanes RE, Ye Z, et al. Epigenomics of human CD8 T cell differentiation and aging. *Sci Immunol.* (2017) 2:eaag0192. doi: 10.1126/sciimmunol.aag0192

59. Czesnikiewicz-Guzik M, Lee W-W, Cui D, Hiruma Y, Lamar DL, Yang Z-Z, et al. T cell subset-specific susceptibility to aging. *Clin. Immunol. (Orlando, Fla).* (2008) 127:107–18. doi: 10.1016/j.clim.2007.12.002

60. Reitsema RD, Boots AMH, van der Geest KSM, Sandovici M, Heeringa P, Brouwer E. CD8+ T Cells in GCA and GPA: bystanders or active contributors? *Front. Immunol.* (2021) 12:654109. doi: 10.3389/fimmu.2021.654109

61. Park CO, Kupper TS. The emerging role of resident memory T cells in protective immunity and inflammatory disease. *Nat Med.* (2015) 21:688–97. doi: 10.1038/nm.3883

62. Zhang H, Watanabe R, Berry GJ, Tian L, Goronzy JJ, Weyand CM. Inhibition of JAK-STAT signaling suppresses pathogenic immune responses in medium and large vessel vasculitis. *Circulation.* (2018) 137:1934–48. doi: 10.1161/CIRCULATIONAHA.117.030423

63. Akiyama M, Ohtsuki S, Berry GJ, Liang DH, Goronzy JJ, Weyand CM. Innate and adaptive immunity in giant cell arteritis. *Front Immunol.* (2020) 11:621098. doi: 10.3389/fimmu.2020.621098

64. Espinoza LR, Jara LJ, Silveira LH, Martinez-Osuna P, Zwolinska JB, Kneer C, et al. Anticardiolipin antibodies in polymyalgia rheumatica-giant cell arteritis: association with severe vascular complications. *Am J Med.* (1991) 90:474–8. doi: 10.1016/0002-9343(91)90608-Z

65. Salvarani C, Baricchi R, Macchioni P, Carbognani R, Morelli A, Lodi L, et al. Anticardiolipin antibodies in northern Italian population with PMR/GCA. *Am J Med.* (1992) 92:712–4. doi: 10.1016/0002-9343(92)90803-J

66. Cid MC, Cervera R, Font J, Lopez-Soto A, Pallares L, Navarro M, et al. Late thrombotic events in patients with temporal arteritis and anticardiolipin antibodies. *Clin Exp Rheumatol.* (1990) 8:359–63.

67. Maleszewski JJ, Younge BR, Fritzlen JT, Hunder GG, Goronzy JJ, Warrington KJ, et al. Clinical and pathological evolution of giant cell arteritis: a prospective study of follow-up temporal artery biopsies in 40 treated patients. *Modern Pathology.* (2017) 30:788–96. doi: 10.1038/modpathol.2017.10

68. Ciccia F, Rizzo A, Maugeri R, Alessandro R, Croci S, Guggino G, et al. Ectopic expression of CXCL13, BAFF, APRIL and LT-β is associated with artery tertiary lymphoid organs in giant cell arteritis. *Ann Rheum Dis.* (2017) 76:235–43. doi: 10.1136/annrheumdis-2016-209217

69. van der Geest KS, Abdulahad WH, Chalan P, Rutgers A, Horst G, Huitema MG, et al. Disturbed B cell homeostasis in newly diagnosed giant cell arteritis and polymyalgia rheumatica. *Arthritis Rheumatol (Hoboken, NJ).* (2014) 66:1927–38. doi: 10.1002/art.38625

70. Graver JC, Boots AMH, Haacke EA, Diepstra A, Brouwer E, Sandovici M. Massive B-cell infiltration and organization into artery tertiary lymphoid organs in the aorta of large vessel giant cell arteritis. *Front Immunol.* (2019) 10:83. doi: 10.3389/fimmu.2019.00083

71. Camporeale A, Poli V. IL-6, IL-17 and STAT3: a holy trinity in auto-immunity? *Front Biosci (Landmark Ed).* (2012) 17:2306–26. doi: 10.2741/4054

72. Saravia J, Chapman NM, Chi H. Helper T cell differentiation. *Cell Mol Immunol.* (2019) 16:634–43. doi: 10.1038/s41423-019-0220-6

73. Rutz S, Eidenschenk C, Ouyang W. IL-22, not simply a Th17 cytokine. *Immunol Rev.* (2013) 252:116–32. doi: 10.1111/imr.12027

74. Torchinsky MB, Blander JM, T. helper 17 cells: discovery, function, and physiological trigger. *Cell Mol Life Sci.* (2010) 67:1407–21. doi: 10.1007/s00018-009-0248-3

75. Nizzoli G, Krietsch J, Weick A, Steinfelder S, Facciotti F, Gruarin P, et al. Human CD1c+ dendritic cells secrete high levels of IL-12 and potently prime cytotoxic T-cell responses. *Blood.* (2013) 122:932–42. doi: 10.1182/blood-2013-04-495424

76. Fenton SE, Saleiro D, Platanias LC. Type I and II interferons in the anti-tumor immune response. *Cancers (Basel).* (2021) 13:1037. doi: 10.3390/cancers13051037

77. Bai Y, Ahmad U, Wang Y, Li JH, Choy JC, Kim RW, et al. Interferon-gamma induces X-linked inhibitor of apoptosis-associated factor-1 and Noxa expression and potentiates human vascular smooth muscle cell apoptosis by STAT3 activation. *J Biol Chem.* (2008) 283:6832–42. doi: 10.1074/jbc.M706021200

78. Wadström K, Jacobsson LTH, Mohammad AJ, Warrington KJ, Matteson EL, Jakobsson ME, et al. Analyses of plasma inflammatory proteins reveal biomarkers predictive of subsequent development of giant cell arteritis: a prospective study. *Rheumatology (Oxford, England).* (2022). doi: 10.1093/rheumatology/keac581

79. Lafferty KJ, Cunningham AJ, A. new analysis of allogeneic interactions. *Aust J Exp Biol Med Sci.* (1975) 53:27–42. doi: 10.1038/icb.1975.3

80. Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. *Annu Rev Immunol.* (2008) 26:677–704. doi: 10.1146/annurev.immunol.26.021607.090331

81. Ramos-Casals M, Brahmer JR, Callahan MK, Flores-Chávez A, Keegan N, Khamashta MA, et al. Immune-related adverse events of checkpoint inhibitors. *Nat Rev Dis Primers.* (2020) 6:38. doi: 10.1038/s41572-020-0160-6

82. Kreuter A, Koushk-Jalali B, Cusenza A, Oellig F, Tigges C. Nivolumab-associated giant cell arteritis with scalp necrosis. *JAMA Dermatol.* (2019) 155:1086–7. doi: 10.1001/jamadermatol.2019.1411

83. Betrains A, Blockmans DE. Immune checkpoint inhibitor-associated polymyalgia rheumatica/giant cell arteritis occurring in a patient after treatment with nivolumab. *JCR: J Clin Rheumatol.* (2021) 27:S555-6. doi: 10.1097/RHU.0000000000001012

84. Narala R, Reddy SA, Mruthyunjaya P. Giant cell arteritis manifesting as retinal arterial occlusion and paracentral acute middle maculopathy in a patient on pembrolizumab for metastatic uveal melanoma. *Am J Ophthalmol Case Rep.* (2020) 20:100891. doi: 10.1016/j.ajoc.2020.100891

85. Micaily I, Chernoff M. An unknown reaction to pembrolizumab: giant cell arteritis. *Ann Oncol.* (2017) 28:2621–2. doi: 10.1093/annonc/mdx306

86. Watanabe R, Zhang H, Berry G, Goronzy JJ, Weyand CM. Immune checkpoint dysfunction in large and medium vessel vasculitis. *Am J Physiol Heart Circ Physiol.* (2017) 312:H1052–h9. doi: 10.1152/ajpheart.00024.2017

87. Zhang H, Watanabe R, Berry GJ, Vaglio A, Liao YJ, Warrington KJ, et al. Immunoinhibitory checkpoint deficiency in medium and large vessel vasculitis. *Proc Natl Acad Sci U S A.* (2017) 114:E970–e9. doi: 10.1073/pnas.1616848114

88. Zhang X, Niessner A, Nakajima T, Ma-Krupa W, Kopecky SL, Frye RL, et al. Interleukin 12 induces T-cell recruitment into the atherosclerotic plaque. *Circ Res.* (2006) 98:524–31. doi: 10.1161/01.RES.0000204452.46568.57

89. Watanabe R, Shirai T, Namkoong H, Zhang H, Berry GJ, Wallis BB, et al. Pyruvate controls the checkpoint inhibitor PD-L1 and suppresses T cell immunity. *J Clin Invest.* (2017) 127:2725–38. doi: 10.1172/JCI92167

90. Ungprasert P, Upala S, Sanguankeo A, Warrington KJ. Patients with giant cell arteritis have a lower prevalence of diabetes mellitus: a systematic review and meta-analysis. *Modern Rheumatol.* (2016) 26:410–4. doi: 10.3109/14397595.2015.1081722

91. Wadström K, Jacobsson L, Mohammad AJ, Warrington KJ, Matteson EL, Turesson C. Negative associations for fasting blood glucose, cholesterol and triglyceride levels with the development of giant cell arteritis. *Rheumatology.* (2020) 59:3229–36. doi: 10.1093/rheumatology/keaa080

92. van Sleen Y, Sandovici M, Abdulahad WH, Bijzet J, van der Geest KSM, Boots AMH, et al. Markers of angiogenesis and macrophage products for predicting disease course and monitoring vascular inflammation in giant cell arteritis. *Rheumatology (Oxford, England).* (2019) 58:1383–92. doi: 10.1093/rheumatology/kez034

93. Baldini M, Maugeri N, Ramirez GA, Giacomassi C, Castiglioni A, Prieto-González S, et al. Selective up-regulation of the soluble pattern-recognition receptor pentraxin 3 and of vascular endothelial growth factor in giant cell arteritis: relevance for recent optic nerve ischemia. *Arthritis Rheum.* (2012) 64:854–65. doi: 10.1002/art.33411

94. Wen Z, Shen Y, Berry G, Shahram F, Li Y, Watanabe R, et al. The microvascular niche instructs T cells in large vessel vasculitis via the VEGF-Jagged1-Notch pathway. *Sci Transl Med.* (2017) 9:eaal3322. doi: 10.1126/scitranslmed.aal3322

95. Piggott K, Deng J, Warrington K, Younge B, Kubo JT, Desai M, et al. Blocking the NOTCH pathway inhibits vascular inflammation in large-vessel vasculitis. *Circulation.* (2011) 123:309–18. doi: 10.1161/CIRCULATIONAHA.110.936203

96. Planas-Rigol E, Terrades-Garcia N, Corbera-Bellalta M, Lozano E, Alba MA, Segarra M, et al. Endothelin-1 promotes vascular smooth muscle cell migration across the artery wall: a mechanism contributing to vascular

remodelling and intimal hyperplasia in giant-cell arteritis. *Ann Rheum Dis.* (2017) 76:1624. doi: 10.1136/annrheumdis-2016-210792

97. Mammoto A, Matus K, Mammoto T. Extracellular Matrix in Aging Aorta. *Front Cell Dev Biol*. (2022) 10:822561. doi: 10.3389/fcell.2022.822561

98. Ilarregui JM, Rabinovich GA. Tolerogenic dendritic cells in the control of autoimmune neuroinflammation: an emerging role of protein-glycan interactions. *Neuroimmunomodulation.* (2010) 17:157–60. doi: 10.1159/000258712

99. Kennedy BK, Berger SL, Brunet A, Campisi J, Cuervo AM, Epel ES, et al. Geroscience: linking aging to chronic disease. *Cell.* (2014) 159:709–13. doi: 10.1016/j.cell.2014.10.039

100. Franceschi C, Garagnani P, Parini P, Giuliani C, Santoro A. Inflammaging: a new immune-metabolic viewpoint for age-related diseases. *Nat Rev Endocrinol.* (2018) 14:576–90. doi: 10.1038/s41574-018-0059-4

101. Agrawal A, Agrawal S, Gupta S. Role of dendritic cells in inflammation and loss of tolerance in the elderly. *Front Immunol.* (2017) 8:896. doi: 10.3389/fimmu.2017.00896

102. Weyand CM, Fulbright JW, Goronzy JJ. Immunosenescence, autoimmunity, and rheumatoid arthritis. *Exp Gerontol.* (2003) 38:833–41. doi: 10.1016/S0531-5565(03)00090-1

103. Goronzy JJ, Weyand CM. Understanding immunosenescence to improve responses to vaccines. *Nat Immunol.* (2013) 14:428–36. doi: 10.1038/ni.2588

104. Eva M-R, Maria Carolina F. Understanding intrinsic hematopoietic stem cell aging. *Haematologica.* (2020) 105:22–37. doi: 10.3324/haematol.2018.211342

105. Gruver AL, Hudson LL, Sempowski GD. Immunosenescence of ageing. *J Pathol.* (2007) 211:144–56. doi: 10.1002/path.2104

106. Hale LP. Histologic and molecular assessment of human thymus. *Ann Diagn Pathol.* (2004) 8:50–60. doi: 10.1016/j.anndiagpath.2003.11.006

107. Nikolich-Žugich J, Bradshaw CM, Uhrlaub JL, Watanabe M. Immunity to acute virus infections with advanced age. *Curr Opin Virol.* (2021) 46:45–58. doi: 10.1016/j.coviro.2020.09.007

108. Decman V, Laidlaw BJ, Doering TA, Leng J, Ertl HC, Goldstein DR, et al. Defective CD8 T cell responses in aged mice are due to quantitative and qualitative changes in virus-specific precursors. *J Immunol.* (2012) 188:1933–41. doi: 10.4049/jimmunol.1101098

109. Maly K, Schirmer M. The story of CD4+ CD28- T cells revisited: solved or still ongoing? *J Immunol Res.* (2015) 2015:348746. doi: 10.1155/2015/348746

110. Warrington KJ, Vallejo AN, Weyand CM, Goronzy JJ. CD28 loss in senescent CD4+ T cells: reversal by interleukin-12 stimulation. *Blood.* (2003) 101:3543–9. doi: 10.1182/blood-2002-08-2574

111. Vallejo AN, Nestel AR, Schirmer M, Weyand CM, Goronzy JJ. Aging-related deficiency of CD28 expression in CD4+ T cells is associated with the loss of gene-specific nuclear factor binding activity. *J Biol Chem.* (1998) 273:8119–29. doi: 10.1074/jbc.273.14.8119

112. Schmidt D, Goronzy JJ, Weyand CM. CD4+ CD7- CD28- T cells are expanded in rheumatoid arthritis and are characterized by autoreactivity. *J Clin Invest.* (1996) 97:2027–37. doi: 10.1172/JCI 118638

113. Weyand CM, Brandes JC, Schmidt D, Fulbright JW, Goronzy JJ. Functional properties of CD4+ CD28- T cells in the aging immune system. *Mech Ageing Dev.* (1998) 102:131–47. doi: 10.1016/S0047-6374(97)00161-9

114. Dejaco C, Duftner C, Al-Massad J, Wagner AD, Park JK, Fessler J, et al. NKG2D stimulated T-cell autoreactivity in giant cell arteritis and polymyalgia rheumatica. *Ann Rheum Dis.* (2013) 72:1852–9. doi: 10.1136/annrheumdis-2012-201660

115. 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 Takayasu Arteritis. *Arthritis Rheumatol (Hoboken, NJ).* (2017) 69:846–53. doi: 10.1002/art.40037

116. Weksler ME, Szabo P. The effect of age on the B-cell repertoire. *J Clin Immunol.* (2000) 20:240–9. doi: 10.1023/A:1006659401385

117. Panda A, Arjona A, Sapey E, Bai F, Fikrig E, Montgomery RR, et al. Human innate immunosenescence: causes and consequences for immunity in old age. *Trends Immunol.* (2009) 30:325–33. doi: 10.1016/j.it.2009.05.004

118. Adrover JM, Nicolás-Ávila JA, Hidalgo A. Aging: a temporal dimension for neutrophils. *Trends Immunol.* (2016) 37:334–45. doi: 10.1016/j.it.2016.03.005

119. Born J, Uthgenannt D, Dodt C, Nünninghoff D, Ringvolt E, Wagner T, et al. Cytokine production and lymphocyte subpopulations in aged humans. An assessment during nocturnal sleep. *Mech Ageing Dev.* (1995) 84:113–26. doi: 10.1016/0047-6374(95)01638-4

120. Michaud M, Balardy L, Moulis G, Gaudin C, Peyrot C, Vellas B, et al. Proinflammatory cytokines, aging, and age-related diseases. *J Am Med Dir Assoc.* (2013) 14:877–82. doi: 10.1016/j.jamda.2013.05.009

121. Salvarani C, Gabriel SE, O'Fallon WM, Hunder GG. The incidence of giant cell arteritis in Olmsted County, Minnesota: apparent fluctuations in a cyclic pattern. *Ann Intern Med.* (1995) 123:192–4. doi: 10.7326/0003-4819-123-3-199508010-00006

122. Elling P, Olsson AT, Elling H. Synchronous variations of the incidence of temporal arteritis and polymyalgia rheumatica in different regions of Denmark; association with epidemics of Mycoplasma pneumoniae infection. *J Rheumatol.* (1996) 23:112–9.

123. Rhee RL, Grayson PC, Merkel PA, Tomasson G. Infections and the risk of incident giant cell arteritis: a population-based, case-control study. *Ann Rheum Dis.* (2017) 76:1031–5. doi: 10.1136/annrheumdis-2016-210152

124. Stamatis P, Turkiewicz A, Englund M, Jönsson G, Nilsson J, Turesson C, et al. Infections are associated with increased risk of giant cell arteritis—a population-based case-control study from Southern Sweden. *J Rheumatol.* (2020). doi: 10.3899/jrheum.200211

125. Gilden D, White T, Khmeleva N, Boyer PJ, Nagel MA, VZV. in biopsy-positive and -negative giant cell arteritis: Analysis of 100+ temporal arteries. *Neurol Neuroimmunol Neuroinflamm.* (2016) 3:e216. doi: 10.1212/NXI.0000000000000216

126. Gabriel SE, Espy M, Erdman DD, Bjornsson J, Smith TF, Hunder GG. The role of parvovirus B19 in the pathogenesis of giant cell arteritis: a preliminary evaluation. *Arthritis Rheum.* (1999) 42:1255–8. doi: 10.1002/1529-0131(199906)42:6<1255::AID-ANR23>3.0.CO;2-P

127. Duhaut P, Bosshard S, Calvet A, Pinede L, Demolombe-Rague S, Dumontet C, et al. Giant cell arteritis, polymyalgia rheumatica, and viral hypotheses: a multicenter, prospective case-control study. Groupe de Recherche sur l'Arterite a Cellules Geantes. *J Rheumatol.* (1999) 26:361–9.

128. Helweg-Larsen J, Tarp B, Obel N, Baslund B. No evidence of parvovirus B19, Chlamydia pneumoniae or human herpes virus infection in temporal artery biopsies in patients with giant cell arteritis. *Rheumatology (Oxford, England).* (2002) 41:445–9. doi: 10.1093/rheumatology/41.4.445

129. Solomon IH, Docken WP, Padera RF. Investigating the association of giant cell arteritis with varicella zoster virus in temporal artery biopsies or ascending aortic resections. *J Rheumatol.* (2019) 46:1614–8. doi: 10.3899/jrheum.180912

130. Sandovici M, van der Geest N, van Sleen Y, Brouwer E. Need and value of targeted immunosuppressive therapy in giant cell arteritis. *RMD Open*. (2022) 8:e001652. doi: 10.1136/rmdopen-2021-001652

131. Stone JH, Spotswood H, Unizony SH, Aringer M, Blockmans D, Brouwer E, et al. New-onset versus relapsing giant cell arteritis treated with tocilizumab: 3-year results from a randomized controlled trial and extension. *Rheumatology (Oxford, England).* (2022) 61:2915–22. doi: 10.1093/rheumatology/keab780

132. Venhoff N, Schmidt W, Bergner R, Rech J, Unger L, Tony H, et al. Secukinumab in giant cell arteritis: a randomized, parallel-group, double-blind, placebo-controlled, multicenter phase 2 trial. ACR convergence 2021. Virtual congress. *Arthritis Rheumatol*. (2021) 73.

133. Cid MC, Unizony SH, Blockmans D, Brouwer E, Dagna L, Dasgupta B, et al. Efficacy and safety of mavrilimumab in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis.* (2022) 81:653–61. doi: 10.1136/annrheumdis-2021-221865

134. Koster MJ, Crowson CS, Giblon RE, Jaquith JM, Duarte-García A, Matteson EL, et al. Baricitinib for relapsing giant cell arteritis: a prospective open-label 52-week pilot study. *Ann Rheum Dis.* (2022) 81:861–7. doi: 10.1136/annrheumdis-2021-221961

135. Stamatis P, Turesson C, Willim M, Nilsson J-Å, Englund M, Mohammad AJ. Malignancies In giant cell arteritis: a population-based cohort study. *J Rheumatology*. (2019) 2019:jrheum.190236. doi: 10.3899/jrheum.190236

136. Brekke LK, Fevang BS, Diamantopoulos AP, Assmus J, Esperø E, Gjesdal CG. Risk of cancer in 767 patients with giant cell arteritis in western norway: a retrospective cohort with matched controls. *J Rheumatol.* (2020) 47:722–9. doi: 10.3899/jrheum.190147

137. Xu S, Lai R, Zhao Q, Zhao P, Zhao R, Guo Z. Correlation between immune-related adverse events and prognosis in hepatocellular carcinoma patients treated with immune checkpoint inhibitors. *Front Immunol.* (2021) 12:794099. doi: 10.3389/fimmu.2021.794099

138. Tang K, Seo J, Tiu BC, Le TK, Pahalyants V, Raval NS, et al. Association of cutaneous immune-related adverse events with increased survival in patients treated with anti-programmed cell death 1 and anti-programmed cell death ligand 1 therapy. *JAMA Dermatol.* (2022) 158:189–93. doi: 10.1001/jamadermatol.2021.5476

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REVIEWED BY
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Lund University, Sweden
Prasanta Padhan,
Kalinga Institute of Medical Sciences (KIMS), India
Geirmund Myklebust,
Hospital of Southern Norway, Norway

*CORRESPONDENCE
Suellen A. Lyne
Suellen.Lyne@adelaide.edu.au

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Giant cell arteritis: A population-based retrospective cohort study exploring incidence and clinical presentation in Canterbury, Aotearoa New Zealand

Suellen A. Lyne[1,2,3]*, Carlee Ruediger[1,2], Susan Lester[1,2], Peter T. Chapman[4], Ernst Michael Shanahan[3,5], Catherine L. Hill[1,2,6] and Lisa Stamp[4,7]

[1]School of Medicine, University of Adelaide, Adelaide, SA, Australia, [2]Department of Rheumatology, The Queen Elizabeth Hospital, Adelaide, SA, Australia, [3]Department of Rheumatology, Flinders Medical Centre, Adelaide, SA, Australia, [4]Department of Rheumatology, Te Whatu Ora Waitematā, Christchurch, New Zealand, [5]College of Medicine and Public Health, Flinders University, Adelaide, SA, Australia, [6]Department of Rheumatology, Royal Adelaide Hospital, Adelaide, SA, Australia, [7]School of Medicine, University of Otago, Christchurch, New Zealand

Background/aim: To determine the epidemiology and clinical features of giant cell arteritis (GCA) in Canterbury, Aotearoa New Zealand, with a particular focus on extra-cranial large vessel disease.

Methods: Patients with GCA were identified from radiology and pathology reports, outpatient letters and inpatient hospital admissions in the Canterbury New Zealand from 1 June 2011 to 31 May 2016. Data was collected retrospectively based on review of electronic medical records.

Results: There were 142 cases of GCA identified. 65.5% of cases were female with a mean age of 74.2 years. The estimated population incidence for biopsy-proven GCA was 10.5 per 100,000 people over the age of 50 and incidence peaked between 80 and 84 years of age. 10/142 (7%) people were diagnosed with large vessel GCA, often presenting with non-specific symptoms and evidence of vascular insufficiency including limb claudication, vascular bruits, blood pressure and pulse discrepancy, or cerebrovascular accident. Those with limited cranial GCA were more likely to present with the cardinal clinical features of headache and jaw claudication. Patients across the two groups were treated similarly, but those with large vessel disease had greater long-term steroid burden. Rates of aortic complication were low across both groups, although available follow-up data was limited.

Conclusion: This study is the first of its kind to describe the clinical characteristics of large vessel GCA in a New Zealand cohort. Despite small

case numbers, two distinct subsets of disease were recognized, differentiating patients with cranial and large vessel disease. Our results suggest that utilization of an alternative diagnostic and therapeutic approach may be needed to manage patients with large vessel disease.

KEYWORDS

epidemiology, giant cell arteritis, incidence, vasculitis, large vessel vasculitis (LVV)

Introduction

Giant Cell Arteritis (GCA) is the most common vasculitis affecting people over the age of 50 years. Highest rates are observed in people with Scandinavian ancestry and epidemiological characteristics have been well-described in large populations across Europe and Northern America (1, 2). Little work has been published on the epidemiology of GCA in Aotearoa New Zealand (NZ). One retrospective cohort study reported a mean annual incidence of 12.7 per 100,000 over the age of 50 for biopsy-proven GCA (3) and a recent study assessing diagnostic performance of color duplex ultrasound reported an incidence in NZ Europeans and Māori of 13.2 and 12.2, respectively (4). Additional work has been conducted exploring seasonal influence on rates of GCA in NZ, with no meaningful trends identified (5).

GCA is a clinically heterogenous disease characterized by granulomatous inflammation of medium and large vessels. Traditionally described as a disease of the temporal arteries, it is now understood to be a systemic disease involving the aorta and any of its major tributaries (6–8). Three primary disease subtypes are recognized: classical or "pure" cranial GCA (C-GCA); extracranial manifestations in the context of established cranial disease; or isolated extracranial large vessel disease without cranial manifestations. The latter two are both designated large vessel GCA (LV-GCA). Each of these phenotypes may occur with or without co-existent symptoms of polymyalgia rheumatica (PMR) (9).

The extent and distribution of vascular involvement in LV-GCA can vary considerably and presenting symptoms are often non-specific. Diagnosis may be difficult as LV-GCA patients are less likely to yield a positive temporal artery biopsy (TAB) and less likely to meet the 1990 American College of Rheumatology (ACR) classification criteria for a diagnosis of GCA, which rely heavily on cranial manifestations (10, 11). Patients with GCA are 17 times more likely to develop thoracic aortic aneurysm compared to age and sex-matched controls and occurrence of this complication is associated with increased mortality (12, 13). Detection of LV involvement is crucial because complications are potentially catastrophic and may not present until years after diagnosis (14–16).

Despite increased awareness of LV involvement in GCA and its potential complications, there is still a paucity of knowledge regarding true incidence rates, implications on treatment strategies and surveillance of long term sequelae. To our knowledge, characteristics of extracranial manifestations, irrespective of cranial involvement, have never been described in a NZ cohort. This proposed research seeks to further our understanding of the epidemiology, clinical manifestations, and complications GCA in NZ, with a particular focus on extra-cranial disease, thereby guiding future screening and management protocols.

Materials and methods

Study design

This retrospective cohort study included incident cases of GCA diagnosed in the Te Whatu Ora Waitaha Canterbury (formerly Canterbury District Health Board) between 1 June 2011 and 31 May 2016. This study was developed in consultation with Māori researcher groups and was approved by the University of Otago, Human Research Ethics Committee (Reference: H21/065).

Inclusion and exclusion criteria

All male and female patients with incident GCA were included. Fulfillment of the 1990 American College of Rheumatology (ACR) classification criteria (10) was not required, with the exception of age $>$ 50, as these criteria are known to preclude patients with isolated extra-cranial disease (11). A positive temporal artery biopsy (TAB) was not required; however, a diagnosis of biopsy-negative GCA had to be confirmed by the treating Rheumatologist, Ophthalmologist, Neurologist, or General Physician. Patients were excluded if an alternative cause for large vessel vasculitis (LVV), such as Takayasu, was confirmed or suspected.

Case identification

Case identification was based on keyword search of radiology reports, histopathology reports and rheumatology

outpatient letters, as well as International Coding of Disease (ICD) classification for inpatient admissions. Keywords included "*temporal arteritis*," "*giant cell arteritis*," "*arteritis*," "*aortitis*," "*vasculitis*," *and* "*Takayasu*." Radiology reports were derived from all imaging modalities at Christchurch Hospital as well as private radiology providers within Canterbury. Features compatible with a diagnosis of vasculitis included circumferential wall thickening, with or without contrast enhancement, and/or vascular stenosis/occlusion, and/or vascular dilation/aneurysm. It was the final opinion of the radiologist that determined the assignment of a positive or negative study. All histopathology reports from Canterbury Health Laboratories were reviewed, except skin and renal specimens, which limited results returning with small vessel vasculitis. Once cases were identified, available electronic medical records were reviewed to confirm the diagnosis of GCA.

Data collection

Data collection included demographics, time to diagnosis, presenting clinical features, biopsy and laboratory results, distribution of large vessel involvement, disease complications, treatment, and treatment related outcomes. Duration of follow-up was determined by the last clinical encounter, up until 31 May 2021, allowing a minimum 5-year follow-up for all patients. Refer to **Supplementary File 1** for the data extraction table.

Study definitions

For the purposes of the study, patients were classified into two groups: those with limited cranial GCA (C-GCA) and those with extra-cranial large vessel GCA (LV-GCA). The latter was defined by the presence of extra-cranial vasculitis on imaging or histopathology, as designated by the reporting radiologist or pathologist. Clinical features suggesting large vessel disease included upper or lower limb claudication, vascular bruits, blood pressure or peripheral pulse discrepancy, aortic aneurysm, dissection or rupture, evidence of ischemic sequelae or end organ infarction due to large vessel stenosis (17).

Statistical analysis

Descriptive data are presented as frequencies and percentages for categorical variables and mean with standard deviation (SD) for continuous variables. The frequency of a specific feature is stated as the number of cases with that feature/number of cases in which the feature was detailed, except in the case of clinical symptoms, where symptoms that were not reported were assumed to be absent. Univariate analysis using Fisher's Exact test was used to study categorical variables. *T*-tests were used to compare the mean age at diagnosis. Mean incidence rate was estimated by Poisson regression, based on 2013 census data available through *Tatauranga Aotearoa*.[1] Stata software (17.0, StataCorp LLC, College Station, TX) was used for data synthesis. All significance tests were two-tailed and values of $p < 0.05$ were considered significant.

Results

One hundred forty-two patients with incident GCA were identified in the study period. 100 (70.4%) were biopsy-proven GCA; of the remaining 42 cases, 7 did not undergo a biopsy, 2 were technically unsuccessful and 33 had negative biopsies. The mean annual incidence for biopsy-proven GCA (n = 100) was 10.5 (95% CI 8.7, 12.8) per 100,000 over the age of 50, and this increased to 15 (95% CI 12.6, 17.6) when all cases were included (n = 142). Patients were predominantly female (65.5%), with a mean ± SD age at diagnosis of 74.2 ± 8.9 years. Incidence rates were highest after 65 years of age and peaked between 80 and 84 years (**Figure 1**).

10/142 (7%) had LV-GCA confirmed on imaging and 7 of the remaining 132 patients with limited C-GCA had symptoms suggestive of possible extra-cranial involvement, but without confirmation on imaging or histopathology. Baseline characteristics of the LV-GCA and C-GCA cohorts are summarized in **Table 1**. There was no statistically significant difference in baseline demographics between the two groups. The mean delay from symptom onset to diagnosis was longer in the LV-GCA group at 11.6 weeks, compared to 6.7 weeks, although statistical significance was not met (p = 0.08). Patients with C-GCA were more likely to present with headache and jaw claudication, while those with LV-GCA were more likely to experience weight loss, upper limb claudication, vascular bruits, blood pressure and pulse discrepancy or cerebrovascular accident. There was no difference in baseline laboratory parameters including CRP, ESR, platelet count and hemoglobin. Those with C-GCA were more likely to undergo a TAB (p = 0.008), but there was no difference in the rate of biopsy positivity between the two groups (p = 0.38). Only 50% of the patients with LV-GCA fulfilled the 1990 ACR classification criteria, which was significantly less than the 82% seen the C-GCA group (p = 0.03).

Imaging modalities used to detect LV-GCA were computed tomography angiography (CT-A), magnetic resonance angiography (MR-A), and ultrasound (US), with 7, 4, and 1 studies, respectively, positive. Imaging was conducted either to evaluate symptoms of vascular disease, such as stroke or limb claudication, or as work up for pyrexia of unknown origin (PUO) (n = 2). Arterial involvement was most frequently

1 https://www.stats.govt.nz/

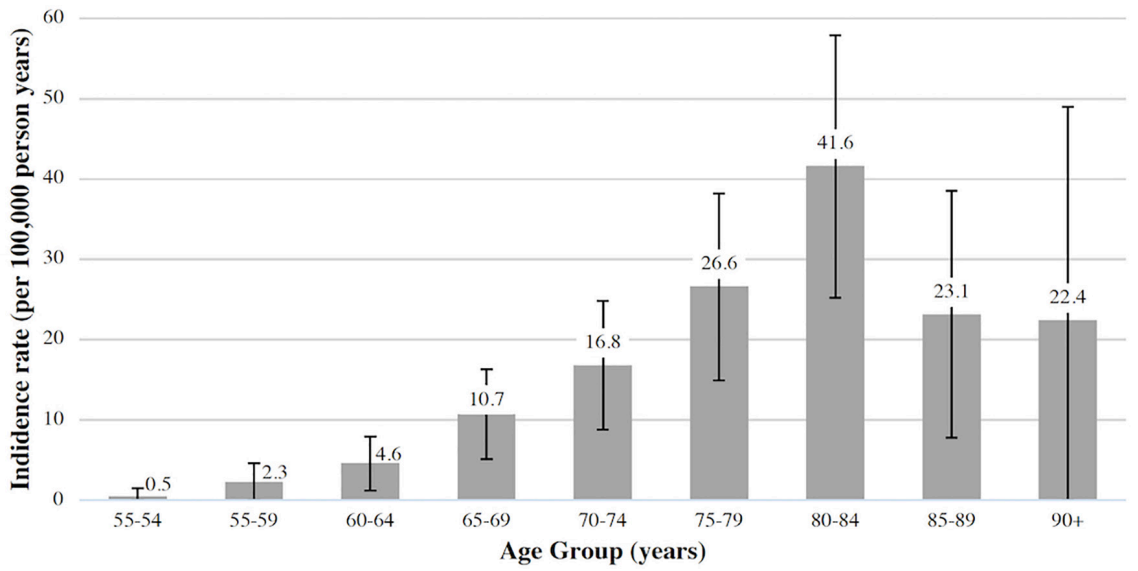

FIGURE 1
Incidence of biopsy-proven giant cell arteritis (GCA) in Canterbury (adjusted for age and sex, 95% CI).

detected in the proximal branches of the aorta, with brachial, axillary and vertebral most frequently involved. Of those with imaging of the brachial arteries 83% were positive, 66.7% for axillary arteries and 80% for vertebral arteries (Figure 2).

Patients with LV- and C-GCA were universally managed with corticosteroid therapy, with no difference in starting dose of oral prednisolone. There was also no difference in the number of patients requiring intravenous (IV) methylprednisolone, although indications differed. Of the two LV-GCA patients requiring IV methylprednisolone, one was for management of arm ischemia and the other was for a posterior circulation stroke with co-existent vision impairment secondary to central retinal artery occlusion (CRAO). IV Methylprednisolone in the C-GCA group was exclusively used for visual disturbance.

Follow-up data was limited, as information was not available for patients discharged to the care of their General Practitioner (GP). Available data suggests those with LV-GCA were more likely to continue prednisolone 5 years after diagnosis compared to C-GCA patients (p = 0.007) (Table 2). Of those continuing prednisolone, there was no difference in mean dose between the two groups at 1-, 3-, and 5-years of follow-up. Use of an alternative immunosuppression was typically reserved for patients with refractory PMR symptoms. Methotrexate was the treatment of choice, with two C-GCA patients also receiving leflunomide, noting Tocilizumab was not available for treatment of GCA during the study period.

The mean duration of follow-up was 48.3 months for LV-GCA patients (n = 9) and 31.6 months for C-GCA patients (n = 72) (p = 0.1), of those followed up within the public hospital outpatient setting (Table 3). Irreversible vision loss was seen at similar rates across the two groups, but permanent neurological deficit due to stroke seen at higher rates in the LV-GCA group (p = 0.001). 5 (3.8%) of the C-GCA patients had a known abdominal aortic aneurysm (AAA) and one (0.8%) had a thoracic aortic aneurysm that pre-dated their GCA diagnosis, two of whom required repair during follow-up. Two C-GCA patients develop a new AAA during follow-up, one requiring surgical repair. Two LV-GCA patients were diagnosed thoracic aortic dilation either at diagnosis or during follow-up, not meeting criteria for aneurysm. This rate was significantly higher than that observed in C-GCA patients (p = 0.004). One C-GCA patient developed a Type B thoracic and abdominal aortic dissection, managed conservatively. No dissections were observed in the LV-GCA group.

Discussion

To our knowledge this is the only study to describe clinical characteristics of patients with LV-GCA in Aotearoa New Zealand. Demographics are similar to those previously reported in NZ, with a mean age of 74.2 years, female predominance (incidence ratio 1.59), and primarily affecting those of European descent (93%). The mean annual incidence for biopsy-proven GCA was marginally lower than that reported elsewhere in NZ (3, 4), at 10.5 per 100,000 over the age of 50, but correlates with a large population study from the UK (18), where many NZ Europeans in Canterbury are descendant. There were no differences in demographics between the LV- and C-GCA cohorts, which contrasts existing literature suggesting LV-GCA patients have a younger age at diagnosis (11, 19, 20), and may be a consequence of our small case numbers.

TABLE 1 Baseline characteristic of patients with limited cranial giant cell arteritis (GCA) compared to those with large vessel GCA.

	Large Vessel GCA (n = 10)		Cranial GCA (n = 132)		P-value (<0.05)
Demographics					
Gender (female)	6/10	60%	87/132	65.9%	0.74
Age at diagnosis (mean ± SD)	70.6 ± 9.6		74.5 ± 8.8		0.19
New Zealand European	8/9	88.9%	114/122	93.4%	0.48
Māori	1/9	11.1%	0/122	0%	0.08
Pacifica	0/9	0%	3/122	2.6%	0.81
Presenting clinical features (n/N, %)					
Delay to diagnosis in weeks (mean ± SD)	11.6 ± 8.8		6.7 ± 7.5		0.08
Cranial manifestations	3/10	30%	115/124	92.7%	**<0.001**
Headache	3/10	30%	103/123	83.7%	**0.001**
Jaw claudication	1/10	10%	57/122	46.7%	**0.042**
Scalp tenderness	3/10	30%	70/122	57.4%	0.11
Transient visual disturbance	3/10	30%	41/123	33.3%	1.00
Permanent vision loss	2/10	20%	18/123	14.6%	0.65
Systemic/constitutional manifestations	9/10	90%	89/124	71.8%	0.29
Polymyalgia rheumatica	5/10	50%	68/124	54.8%	1.00
Fever	3/10	30%	35/123	28.5%	1.00
Weight loss	6/10	60%	28/123	22.8%	**0.018**
Cough	3/10	30%	10/123	8.1%	0.059
Features of extra-cranial disease	10/10	100%	7/123	5.7%	**<0.001**
Upper limb claudication	3/10	30%	1/123	0.8%	**0.001**
Lower limb claudication	1/10	10%	2/123	1.6%	0.21
Vascular bruits	3/10	30%	0/123	0%	**<0.001**
Blood pressure discrepancy	2/10	20%	1/123	0.8%	**0.015**
Pulse discrepancy	5/10	50%	0/123	0%	**<0.001**
Aortic aneurysm at diagnosis	2/10	20%	1/123	0.8%	**0.015**
Cerebrovascular accident	3/10	30%	2/123	1.6%	**0.003**
Laboratory tests (mean ± SD)					
CRP (mg/L)	95.4 ± 79.1		91.5 ± 88.5		0.89
ESR (mm/h)	66.3 ± 30.2		53.4 ± 30.8		0.26
Platelets ($\times 10^9$/L)	413.9 ± 152		384.4 ± 158.7		0.57
Hemoglobin (g/L)	112.1 ± 15.7		125.8 ± 24.5		0.08
Temporal artery biopsy					
TAB Performed	7/10	70%	128/132	97%	**0.008**
TAB Positive	4/7	57%	96/128	75%	0.38
1990 ACR criteria					
Fulfilled at least 3/5 ACR criteria	5/5	50%	100/122	82%	**0.030**

The bold numbers are those P values that meet statistical significance (< 0.05).

Clinical features at presentation were different between the two groups. C-GCA patients were more likely to present with the cardinal features of GCA such as headache and jaw claudication, while LV-GCA patients often presented with non-specific symptoms including weight loss and features of vascular insufficiency. Current literature suggests that cranial symptoms are inversely associated with LV involvement (21). Only 50% of our LV-GCA patients fulfilled the 1990 ACR classification criteria for GCA, which relies heavily upon cranial manifestations, indicating these criteria are insensitive for patients with LV disease (10, 22). Atypical presenting features and insensitive classification criteria pose challenges to the detection of disease and likely account for the diagnostic delay among patients with LV-GCA. This observation is well-described in other large cohort studies (11), and although a trend toward diagnostic delay was seen in our LV-GCA cohort, statistical significance was not met. A high index of suspicion is required to diagnose patients presenting with non-specific symptoms. In our cohort patients with LV-GCA were less likely to undergo a biopsy compared to those with

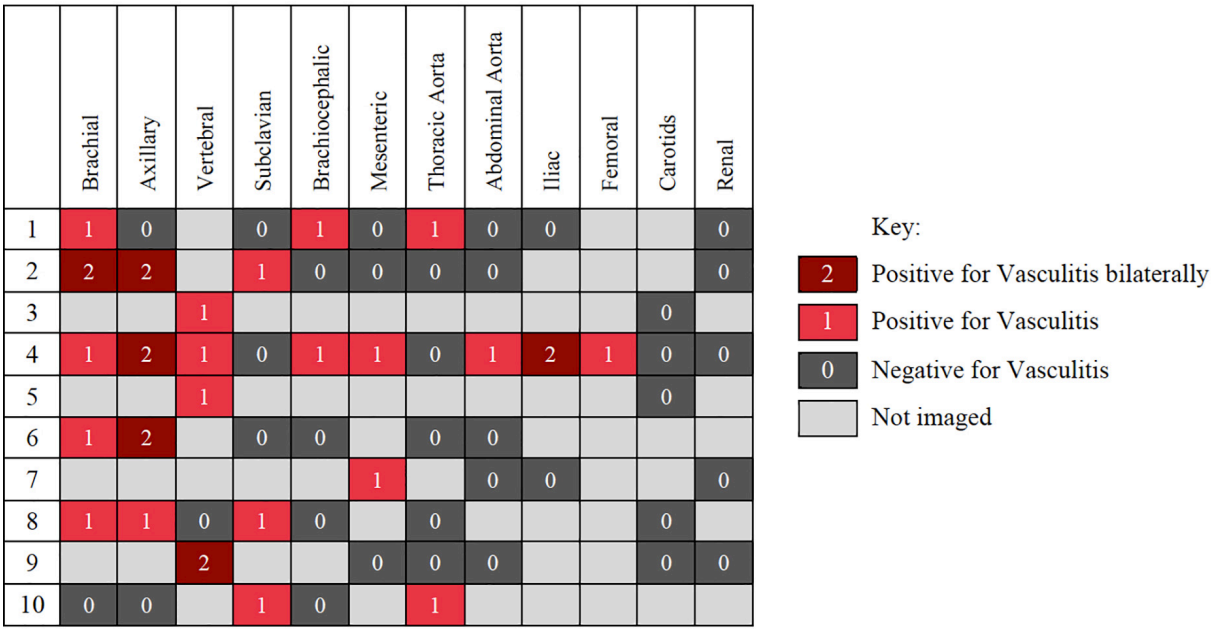

FIGURE 2
Distribution of disease involvement in the 10 patient with large vessels vasculitis detected on computed tomography angiography (CT-A), magnetic resonance angiography (MR-A), and ultrasound (US).

TABLE 2 Comparison of treatment variables in patients with large vessel giant cell arteritis (GCA) and cranial GCA.

	Large Vessel GCA (n = 10)		Cranial GCA (n = 132)		P-value (<0.05)
Treatment					
Starting Prednisolone dose mg (mean ± sd)	52 ± 14.0		59.8 ± 11.8		**0.049**
Need for IV Methylprednisolone at presentation	2/10	20%	14/129	10.9%	0.38
Continuing Prednisolone (n/N, %)					
After 1 year	9/9	100%	87/97	89.7%	0.60
After 3 years	7/9	77.8%	47/86	54.7%	0.29
After 5 years	6/7	85.7%	30/95	31.6%	**0.007**
Mean dose (mg)					
After 1 year	8.8 ± 4.6		10.6 ± 8.2		0.53
After 3 years	8.3 ± 6.3		6.4 ± 5.2		0.45
After 5 years	8.8 ± 6.3		8.7 ± 11.7		0.98
Patients starting an alternative immunosuppressive agent during follow-up (n/N)	2/10	20%	16/130	12.3%	0.62
Methotrexate	2/2	100%	16/16	100%	–
Leflunomide	0/2	0%	2/16	12.5%	–

The bold numbers are those P values that meet statistical significance (< 0.05).

limited cranial disease (p = 0.008); it is unclear whether the decision not to pursue biopsy was due to a low index of disease suspicion or anticipated low test yield. Of those who did undergo a biopsy, there was no difference in rates of biopsy positivity (p = 0.38). This contrasts current literature, which suggests LV-GCA patients are less likely to yield a positive biopsy result (11), posing further challenges to a timely diagnosis.

The extent and distribution of LV involvement can vary considerably and the reason for such a diverse spectrum of disease remains poorly understood. Our results confirm that LV-GCA has a predilection for proximal branches of the aorta (19), with highest rates of vasculitis identified in the upper limb and vertebral arteries. A relatively low number of GCA patients in our cohort had LV vasculitis detected (7%). This figure aligns with earlier GCA studies, where routine imaging

TABLE 3 Comparison of disease outcomes in patients with large vessel GCA (LV-GCA) and cranial GCA (C-GCA).

	Large vessel GCA (n = 10)		Cranial GCA (n = 132)		P-value (<0.05)
Outcomes					
Follow-up data available (n/N)	9/10		72/132		–
Mean Duration of Follow-up (months)	48.3 ± 30		31.6 ± 28		0.1
Disease complications at diagnosis					
Irreversible Vision Loss (n/N,%)	2/10	20%	12/129	9.3%	0.27
Neurological Deficit Due to stroke (n/N,%)	3/10	30%	1/129	0.8%	**0.001**
Aortic complications during follow-up					
Abdominal aortic aneurysm	0/10	0%	2/132	1.5%	1.0
Thoracic aortic dilation	2/10	20%	0/132	0%	**0.004**
Aortic dissection or rupture	0/10	0%	1/132	0.8%	1.0

The bold numbers are those P values that meet statistical significance (< 0.05).

of large vessels was not undertaken and LV-GCA was estimated to account for 3–15% of all GCA cases (8). More recently, prospective studies with dedicated LV imaging have reported rates of LV involvement from 29 to 83% (23, 24). Ongoing variability in reported rates is due to the broad spectrum of clinical presentations, use of various imaging modalities and inconsistent disease definitions. LV imaging of patients with GCA was not routinely conducted in Canterbury during the study period and may explain why detection rates of LV-GCA in our cohort align more closely with earlier GCA studies.

Patients with LV- and C-GCA were universally managed with corticosteroid therapy, with no difference in starting dose of oral prednisolone. Although follow-up data was limited, patients with LV-GCA were more likely to remain on steroids 5 years after diagnosis. This observation is similarly reflected in large cohort studies (25). Current literature is conflicting but suggests that LV-GCA patients may have higher relapse rates compared to C-GCA, with higher cumulative corticosteroids exposure long term (11, 26), and may explain the increased rates of steroid use at 5 years in our LV-GCA cohort. Follow-up data from our study is insufficient to comment on relapse rates, as most relapses were managed by the GP in the primary care setting. Two LV-GCA patients were diagnosed with thoracic aortic dilation, without meeting criteria for aneurysm, a rate significantly higher than that observed in C-GCA patients (p = 0.004). LV-GCA is a recognized risk factor for aortic complications, with potentially catastrophic complications that may not present until years after diagnosis (14–16). Routine screening for LV disease has not been adopted globally, although recent guidelines, including those published by the ACR/Vasculitis Foundation, recommend all patients with newly diagnosed GCA undergo non-invasive vascular imaging to evaluate large vessel involvement and facilitate long term surveillance of potential disease sequelae (27, 28). The resource implications of such an approach, particularly in settings with limited access to advanced imaging, are not insignificant and there remains lack of clear consensus about management and follow-up.

The main limitation of this study is its small case numbers. Only 10 patients with LV-GCA were detected, which limits the statistical power of the analysis and possibly explains the absence of observations that are consistently described in larger cohorts, such as younger age and longer delays to diagnosis for LV-GCA patients. Follow-up data was particularly limited, which is a consequence of the retrospective study design and a reflection of the health care system in NZ, where many chronic diseases are managed in the primary care setting. Another limitation of this study relates to case ascertainment. While it is expected that the majority of patients with GCA were managed in the public healthcare system, and temporal artery biopsies analyzed by Canterbury Health Laboratories, the methods applied for case identification may have missed patients managed privately, or in the primary care setting. The private sector makes up a small portion of the healthcare landscape in NZ. Access was granted to review a representative sample of private patients' case notes, with no cases of GCA identified, suggesting few patients with GCA are seen privately. Numerous methods for case ascertainment were applied to capture such patients; however, it is not possible to quantify how many may have been missed across various sectors. While this number is expected to be small, it may explain why the incidence seen in our cohort is slightly lower than that reported by Abdul-Rahman and Nagarajah (3, 4). Finally, the cases of LV-GCA may suffer from selection bias, as imaging was performed at the discretion of the treating clinician, and therefore only those with symptoms of LV extra-cranial involvement underwent LV imaging. A prospective study with LV imaging of all consecutive GCA patients would be required to eliminate such bias.

This study is the first of its kind to describe the clinical characteristics of patients with LV-GCA in New Zealand. Incidence was comparable to previous NZ studies, and although case numbers were small, two distinct subsets of disease were apparent. Those with cranial disease were more likely to

present with the cardinal clinical features of headache and jaw claudication, while patients with LV-disease often presented with non-specific symptoms including vascular insufficiency and were less likely to fulfill the ACR classification criteria for GCA. In general, treatment approach was similar, however, those with LV-GCA had greater long term steroid burden, suggesting these patients may have a more refractory disease course and require a tailored therapeutic approach. A large prospective study with LV imaging of all consecutive GCA patients is required confirm our findings, but these results suggest that an innovative diagnostic and therapeutic approach may be required to manage patients with large vessel disease.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the University of Otago, Human Research Ethics Committee (Reference: H21/065). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

SAL, LS, SL, CH, PC, CR, and ES: contribution to study conception and design, data analysis and interpretation, drafting the article, critical revision, and final approval of the manuscript. SAL, LS, CH, PC, and CR: contribution to data acquisition. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.1057917/full#supplementary-material

References

1. Li KJ, Semenov D, Turk M, Pope J. A meta-analysis of the epidemiology of giant cell arteritis across time and space. *Arthritis Res Ther.* (2021) 23:82. doi: 10.1186/s13075-021-02450-w

2. Sharma A, Mohammad AJ, Turesson C. Incidence and prevalence of giant cell arteritis and polymyalgia rheumatica: a systematic literature review. *Semin Arthritis Rheum.* (2020) 50:1040–8. doi: 10.1016/j.semarthrit.2020.07.005

3. Abdul-Rahman AM, Molteno AC, Bevin TH. The epidemiology of giant cell arteritis in Otago, New Zealand: a 9-year analysis. *N Z Med J.* (2011) 124:44–52.

4. Nagarajah R, Gupta R, Kumar S. Diagnostic use of ultrasound in giant cell arteritis in Counties Manukau District Health Board, New Zealand. *Rheumatol Adv Pract.* (2022) 6:rkac040. doi: 10.1093/rap/rkac040

5. De Smit E, Clarke L, Sanfilippo PG, Merriman TR, Brown MA, Hill CL, 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:e000531. doi: 10.1136/rmdopen-2017-000531

6. Hutchinson J. Diseases of the arteries. *Arch Surg.* (1890) 1:323–33.

7. Horton BM, Magath TB, Brown GE. An undescribed form of arteritis of the temporal vessels. *Proc Staff Meet Mayo Clinic.* (1932) 7:700–1.

8. Klein RG, Hunder GG, Stanson AW, Sheps SG. Large artery involvement in giant cell (temporal) arteritis. *Ann Intern Med.* (1975) 83:806–12. doi: 10.7326/0003-4819-83-6-806

9. 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. *Rheumatology.* (2017) 56:506–15. doi: 10.1093/rheumatology/kew273

10. Hunder GG, Bloch DA, Michel BA, Stevens MB, Arend WP, Calabrese LH, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. *Arthr Rheum.* (1990) 33:1122–8. doi: 10.1002/art.1780330810

11. Muratore F, Kermani TA, Crowson CS, Green AB, Salvarani C, Matteson EL, et al. Large-vessel giant cell arteritis: a cohort study. *Rheumatology.* (2015) 54:463–70. doi: 10.1093/rheumatology/keu329

12. Evans JM, O'Fallon WM, Hunder GG. Increased incidence of aortic aneurysm and dissection in giant cell (temporal) arteritis: a population-based study.

Ann Intern Med. (1995) 122:502–7. doi: 10.7326/0003-4819-122-7-199504010-00004

13. Nuenninghoff DM, Hunder GG, Christianson TJH, McClelland RL, Matteson EL. Mortality of large-artery complication (Aortic Aneurysm, Aortic Dissection, and/or Large-Artery Stenosis) in Patients with Giant Cell Arteritis: a population-based study over 50 years. *Arthr Rheum.* (2003) 48:3532–7. doi: 10.1002/art.11480

14. Bongartz T, Matteson EL. Large-vessel involvement in giant cell arteritis. *Curr Opin Rheumatol.* (2006) 18:10–7. doi: 10.1097/01.bor.0000197996.04709.4e

15. Nuenninghoff DM, Warrington KJ, Matteson EL. Concomitant giant cell aortitis, thoracic aortic aneurysm, and aortic arch syndrome: occurrence in a patient and significance. *Arthr Rheum.* (2003) 49:858–61. doi: 10.1002/art.11453

16. Gonzalez-Gay MA, Garcia-Porrua C, Pineiro A, Pego-Reigosa R, Llorca J, Hunder GG. Aortic aneurysm and dissection in patients with biopsy-proven giant cell arteritis from northwestern Spain: a population-based study. *Medicine.* (2004) 83:335–41. doi: 10.1097/01.md.0000145366.40805.f8

17. Koster MJ, Matteson EL, Warrington KJ. Large-vessel giant cell arteritis: Diagnosis, monitoring and management. *Rheumatology.* (2018) 57(Suppl. 2):ii32–42. doi: 10.1093/rheumatology/kex424

18. Petri H, Nevitt A, Sarsour K, Napalkov P, Collinson N. Incidence of giant cell arteritis and characteristics of patients: data-driven analysis of comorbidities. *Arthritis Care Res.* (2015) 67:390–5. doi: 10.1002/acr.22429

19. Prieto-González S, Arguis P, García-Martínez A, Espígol-Frigolé G, Tavera-Bahillo I, Butjosa M, et al. Large vessel involvement in biopsy-proven giant cell arteritis: prospective study in 40 newly diagnosed patients using CT angiography. *Ann Rheum Dis.* (2012) 71:1170–6. doi: 10.1136/annrheumdis-2011-200865

20. Brack A, Martinez-Taboada V, Stanson A, Goronzy JJ, Weyand CM. Disease pattern in cranial and large-vessel giant cell arteritis. *Arthr Rheum.* (1999) 42:311–7. doi: 10.1002/1529-0131(199902)42:2<311::AID-ANR14>3.0.CO;2-F

21. Nuenninghoff DM, Hunder GG, Christianson TJ, McClelland RL, Matteson EL. Incidence and predictors of large-artery complication (aortic aneurysm, aortic dissection, and/or large-artery stenosis) in patients with giant cell arteritis: a population-based study over 50 years. *Arthr Rheum.* (2003) 48:3522–31. doi: 10.1002/art.11353

22. Seeliger B, Sznajd J, Robson JC, Judge A, Craven A, Grayson PC, et al. Are the 1990 American College of Rheumatology vasculitis classification criteria still valid? *Rheumatology.* (2017) 56:1154–61. doi: 10.1093/rheumatology/kex075

23. 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) 55:131–7. doi: 10.1002/art.21699

24. Ghinoi A, Pipitone N, Nicolini A, Boiardi L, Silingardi M, Germanò G, et al. Large-vessel involvement in recent-onset giant cell arteritis: a case-control colour-Doppler sonography study. *Rheumatology.* (2012) 51:730–4. doi: 10.1093/rheumatology/ker329

25. Sugihara T, Hasegawa H, Uchida H, Yoshifuji H, Nakaoka Y, Watanabe Y, et al. Characteristics of patients with giant cell arteritis and Takayasu arteritis in a nationwide, retrospective cohort study in Japan. *Rheumatology.* (2017) 56(Supplement 3):iii52–60. doi: 10.1093/rheumatology/kex108

26. Sugihara T, Hasegawa H, Uchida HA, Yoshifuji H, Watanabe Y, Amiya E, et al. Associated factors of poor treatment outcomes in patients with giant cell arteritis: clinical implication of large vessel lesions. *Arthritis Res Ther.* (2020) 22:72. doi: 10.21203/rs.2.22145/v2

27. Maz M, Chung SA, Abril A, Langford CA, Gorelik M, Guyatt G, et al. 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the management of giant cell arteritis and takayasu arteritis. *Arthritis Rheumatol.* (2021) 73:1349–65. doi: 10.1002/art.41774

28. Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE Jr, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM Guidelines for the diagnosis and management of patients with thoracic aortic disease. a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology,American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons,and Society for Vascular Medicine. *J Am Coll Cardiol.* (2010) 55:e27–129.

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EDITED BY
Andreas P. Diamantopoulos,
Akershus University Hospital, Norway

REVIEWED BY
Lene Kristin Brekke,
Haugesund Hospital for Rheumatic Diseases, Norway
Kornelis van der Geest,
University Medical Center Groningen, Netherlands

*CORRESPONDENCE
Catherine L. Hill
catherine.hill@sa.gov.au

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Diagnosis of giant cell arteritis by temporal artery biopsy is associated with biopsy length

Carlee Ruediger[1,2], Jem Ninan[2,3], Kathryn Dyer[1], Suellen Lyne[1,2], Joanna Tieu[1,2,3], Rachel J. Black[1,2,4], Thomas Dodd[5], Susan Lester[1,2,6] and Catherine L. Hill[1,2,4]*

[1]Rheumatology Unit, The Queen Elizabeth Hospital, Woodville South, SA, Australia, [2]Discipline of Medicine, The University of Adelaide, Adelaide, SA, Australia, [3]Rheumatology Unit, Northern Adelaide Local Health Network, Adelaide, SA, Australia, [4]Rheumatology Unit, Royal Adelaide Hospital, Adelaide, SA, Australia, [5]SA Pathology, Adelaide, SA, Australia, [6]Basil Hetzel Institute, Woodville South, SA, Australia

Aims: Temporal artery biopsy (TAB) is a widely used method for establishing a diagnosis of Giant Cell Arteritis (GCA). The optimal TAB length for accurate histological GCA diagnosis has been suggested as 15 mm post-fixation (15–20 mm pre-fixation). The aim of this study was to determine the relationship between a histological GCA diagnosis and optimal TAB length in the South Australian (SA) population.

Materials and methods: Pre-fixation TAB length (mm) was reported in 825/859 of all samples submitted to SA Pathology between 2014 and 2020 from people aged 50 and over. When more than one biopsy was taken, the longest length was recorded. Analyses of both TAB length and TAB positive proportions were performed by multivariable linear and logistic regression analysis, including covariates sex, age, and calendar year.

Results: The median age of participants was 72 (IQR 65, 79) years, 549 (66%) were female. The TAB positive proportion was 172/825 (21%) with a median biopsy length of 14 mm (IQR 9, 18). Biopsy length (mm) was shorter in females (p = 0.001), increased with age (p = 0.006), and a small positive linear trend with calendar year was observed (p = 0.015). The TAB positive proportion was related to older age (slope/decade: 6, 95% CI 3.6, 8.3, $p < 0.001$) and to TAB length (slope/mm 0.6, 95% CI 0.2, 0.9, p = 0.002), but not sex or calendar year. Comparison of models with TAB length cut-points at 5, 10, 15, 20 mm in terms of diagnostic yield, receiver operating characteristics and Akaike Information Criteria confirmed $\geq$ 15 mm as an appropriate, recommended TAB length. However, only 383 (46%) of the biopsies in our study met this criteria. The diagnostic yield at this cut-point was estimated as 25% which equates to an expected additional 30 histologically diagnosed GCA patients.

Conclusion: This study confirms that TAB biopsy length is a determinant of a histological diagnosis of temporal arteritis, and confirms that a TAB length

≥ 15 mm is optimal. Approximately half the biopsies in this study were shorter than this optimal length, which has likely led to under-diagnosis of biopsy-proven GCA in SA. Further work is needed to ensure appropriate TAB biopsy length.

KEYWORDS

giant cell arteritis (GCA), biopsy, vasculitis, diagnosis, temporal arteritis

Background

Giant Cell Arteritis (GCA) is an autoimmune condition causing inflammation of medium and large blood vessels, known as vasculitis. GCA is the most common vasculitis affecting the elderly. When presented with a case suggestive of the diagnosis of GCA, there is a need to initiate further investigations to exclude or confirm the diagnosis, historically based on the criteria set out by the American College of Rheumatology (ACR) (1), and more recently, the additional use of ultrasound and other imaging modalities of affected blood vessels (2).

With a specificity of 100%, a temporal artery biopsy (TAB) with histopathology demonstrating necrotizing arteritis characterized by a predominance of mononuclear cell infiltrates or a granulomatous process with multinucleated giant cells, has been a mainstay for a diagnosis of GCA (3). The average diagnostic yield of TAB for GCA is estimated as 25% (IQR 17, 34) (4), with a recent meta-analysis estimating an average sensitivity of only 77% (5), although this was highly variable with estimates from individual studies ranging between 50 and 95%. Therefore, a negative TAB does not exclude disease. This may in part be attributable to the recognition of extra-cranial disease (large vessel vasculitis) as part of the GCA disease spectrum, and it has been suggested that TAB may have an even lower sensitivity in these patients (6). However, technical aspects of the TAB sampling may also contribute to a decreased sensitivity of TAB for GCA. One such aspect is the presence of "skip lesions," where areas of normal pathology may be interspersed within inflamed sections of the artery, resulting in a false negative result. Indeed, retrospective and prospective examination of TAB specimens have identified skip lesions in TAB from 28% of people with temporal arteritis, with inflammatory foci as small as 330 microns identified (7). Because of these skip lesions, the length of the TAB segment is therefore important. Both the British Society for Rheumatology (8) and the European League Against Rheumatism (9) recommend a TAB length of at least 1 cm (10 mm) which is supported by multiple studies (10–12). Other studies have suggested a minimum TAB length of 5 mm (13, 14) or even 20 mm (15–17) is appropriate. Two studies, which more formally evaluated TAB length in relation to diagnostic sensitivity demonstrated that 1.5 cm (15 mm) was the change point for GCA diagnostic sensitivity (18, 19), concluding that the optimal TAB length for accurate GCA diagnosis is at least 15 mm post-fixation (15–20 mm pre-fixation), with greater lengths unlikely to provide significant additional diagnostic yield. In contrast, other studies have reported no relationship between TAB length and diagnostic yield (20–23).

The aim of this study was to determine the relationship between optimal TAB length and a histopathological diagnosis of GCA in the South Australian (SA) population.

Materials and methods

We retrospectively analyzed the results of all TAB reports from January 2014 to December 2020 for biopsies from people aged 50 years and over submitted to the SA public health sector pathology laboratory (SA Pathology). A total of 859 biopsy reports were reviewed, with 825 (96%) reporting pre-fixation TAB length (mm). When more than one biopsy was taken, the longest length was recorded. Age at biopsy and sex information was also collected on all biopsies. The details of the biopsy report including presence of inflammatory cell infiltrate, presence of Giant cells, disruption of internal elastic media, intimal hyperplasia and involvement of vasa vasorum were taken into account. The final opinion of the pathologist determined the assignment of the biopsy into either positive or negative categories. Although the TAB reports were unstructured, a review of specific details reported in 90 positive TAB indicated that giant cells (n = 70, 78%), intimal hyperplasia (n = 68, 76%), and adventitial inflammation (n = 68, 76%) were frequent findings. Over 80% of positive TAB reported inflammatory infiltrates involving all layers of the temporal artery. Those reporting inflammatory infiltrates without the specific term "transmural infiltration" had other strong characteristics of GCA such as the presence of Giant Cells. A specimen with significant eosinophilic infiltrate was excluded.

Statistical analysis was performed using Statav16 (StataCorp LLC, TX, USA). Multivariable regression analyses were used to determine covariates for TAB length (linear regression), TAB length ≥ 15 mm (logistic regression), and TAB positivity (logistic regression). All analyses included additional covariates sex, age, and calendar year. Both linear and quadratic terms

TABLE 1 Temporal artery biopsy (TAB) study demographics.

Comparison	All	TAB positive	TAB negative	*P*-value
n	825	172 (21%)	653 (79%)	
Female: *n* (%)	549 (66%)	109 (63%)	440 (67%)	0.32[1]
Age: Median (IQR)	72 (65, 79)	76 (71, 81)	71 (63, 79)	<0.001[2]
Biopsy length (mm): Median (IQR)	14 (9, 18)	15 (10.5, 20)	13 (9, 18)	<0.001[2]

[1]Pearson's chi-square.
[2]Wilcoxon rank sum.

were evaluated for the linear covariates age and TAB length, but a quadratic term was only retained for age in the logistic regression model for a TAB positive outcome based on the Akaike Information Criterion (AIC). Results were interpreted as marginal population-averaged predictions of the outcome for each covariate, which for the logistic regression model for TAB outcome, was the predicted proportion of positive TAB results. Additional models for the TAB outcome were estimated with the TAB length covariate dichotomized at 5, 10, 15, and 20 mm, and these models were compared using the AIC, the area under the receiver operating curve (AUC-ROC), and diagnostic yield (positive predictive value, PPV).

Results

The median age at biopsy of the 825 patients included in the study was 76 years, 549 (66%) were female, with 172 (21%) TAB positive (Table 1). The age and sex distribution of TAB positive patients were comparable to that of previous studies of biopsy-proven GCA in South Australia (24). Notably, the number of TAB performed in 2020 (n = 143), the first year of the COVID pandemic, was not decreased compared to previous years (103 TAB in 2019 and 140 in 2018).

The overall median biopsy length was 14 mm (IQR 9, 18). Analysis of biopsy length (mm) using a multivariable linear regression model (Figure 1) demonstrated that biopsy length was shorter in females compared to males (difference: −1.8 mm, 95% CI −2,9, −0.8), increased with older age (0.7 mm/decade, 95% CI 0.2, 1.1), and although variable, there was a smoothed linear trend toward increased length with increasing calendar year (p = 0.015). To put this in context, the difference in TAB length for 2017 onward compared to pre 2017 was 1.4 mm (95% CI 0.37, 2.35), after adjustment for age and sex.

The relationship between a positive TAB and covariates sex, TAB age, TAB year and TAB length were determined using a multivariable logistic regression model, with the best model including a quadratic term for age. Patients with a positive TAB were more likely to be older (median age 76 vs. 71 years, Table 1 and Figure 2), but there was no association with either sex or TAB year (Figure 2). Importantly TAB length (mm) was associated with a positive TAB result in a linear manner. When

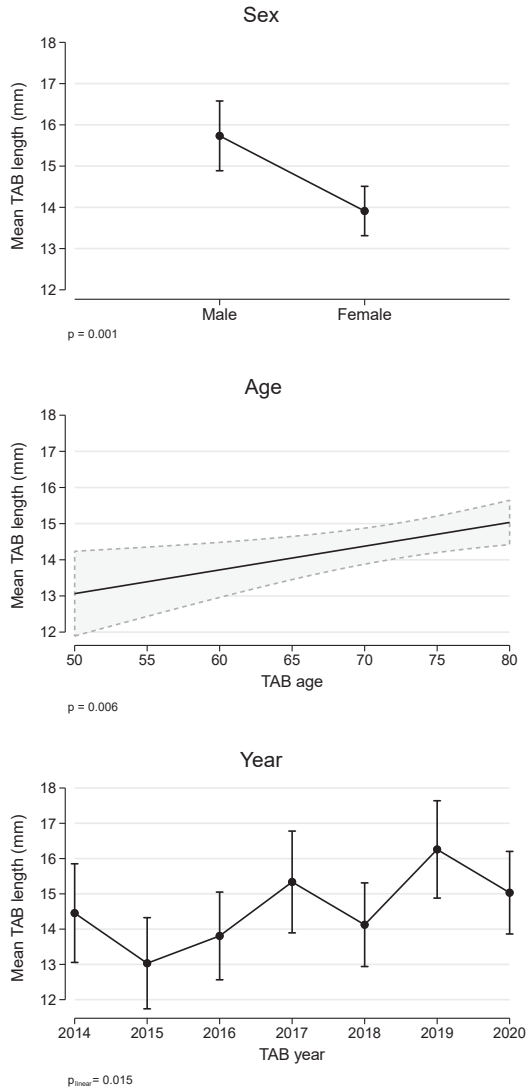

FIGURE 1
Temporal artery biopsy (TAB) length and covariates age, sex, and calendar year (multivariable linear regression). Results are expressed as marginal, population-averaged, outcome means.

adjusted for age, sex, and calendar year, the odds ratio for the association between a positive TAB result and TAB length was 1.04/mm, 95% CI 1.01, 1.06, p = 0.002, which equates in an increase in the marginal probability/proportion of a positive TAB result of 0.6%/mm (95% CI 0.2, 0.9, Figure 2).

Subsequent models compared the effect of dichotomizing TAB length at cut-points 5, 10, 15, and 20 mm on a TAB positive result (Table 2). While the differences were relatively small, the model with TAB length dichotomized at 15 mm was the best model with both the smallest AIC and largest AUC-ROC, however, less than half of the biopsies (383, 46%) in this study met this criteria. The diagnostic yield (positive predictive value) for TAB length ≥ 15 mm was 24.5% (95% CI20.4, 28.7), which,

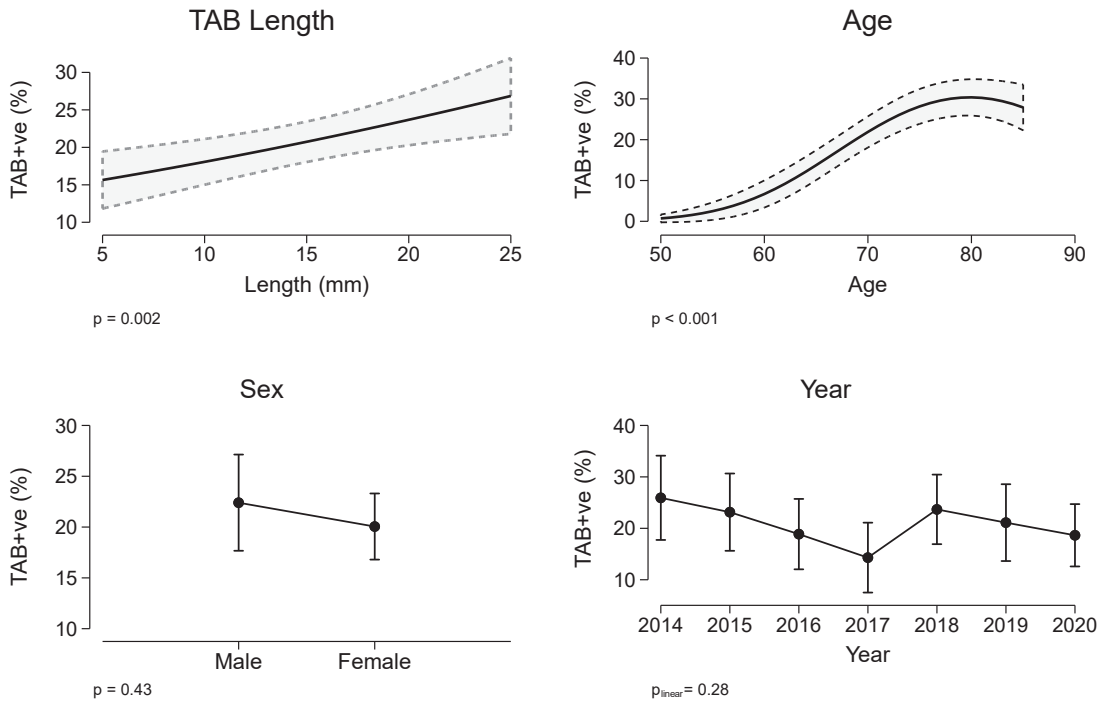

FIGURE 2
Temporal artery biopsy (TAB) positivity and covariates TAB length, sex, age, and year (multivariable logistic regression). Results are expressed as marginal, population-averaged, outcome means.

if all TAB had achieved this length, equates to an average of 30 additional individuals with a diagnosis of biopsy-proven GCA.

Discussion

A suspected diagnosis of GCA may be considered a medical emergency as early diagnosis with treatment intervention can prevent serious complications such as blindness and stroke. A GCA diagnosis is supported by a positive TAB, and increasingly, medical imaging technologies (2), which otherwise can be difficult or delayed because there are no laboratory findings specific for GCA and no particular signs or symptoms specific for the diagnosis. Exclusion of a GCA diagnosis is also important to prevent unnecessary exposure to the adverse effects associated with long-term corticosteroids.

TABLE 2 The relationship between TAB length, dichotomised at 5, 10, 15, and 20 mm, and a positive TAB result.

Descriptor	TAB length (mm)			
	≥ 5 (vs. < 5)	≥ 10 (vs. < 10)	≥ 15 (vs. < 15)	≥ 20 (vs. < 20)
n (%)	798 (97%)	617 (75%)	383 (46%)	192 (23%)
OR (95% CI)	1.85 (0.53, 6.50)	1.66 (1.07, 2.59)	1.57 (1.10, 2.24)	1.52 (1.02, 2.25)
PPV (95% CI)	21.0% (18.3, 23.8)	22.6% (19.5, 25.8)	24.5% (20.4, 28.7)	26.0% (20.1, 31.9)
AUC-ROC (95% CI)	0.682 (0.640, 0.724)	0.689 (0.648, 0.731)	0.692 (0.649, 0.734)	0.690 (0.648, 0.732)
AIC	801.67	797.40	796.59	798.49

OR, odds ratios; PPV, positive predictive values; AUC-ROC, the area under the receiver operating curve; AIC, Akaike information criterion; were estimated from logistic regression models, adjusted for covariates sex, age, and calendar year.

With a specificity of 100%, a positive TAB remains an important tool for the diagnosis of GCA, yet it has a sensitivity of only 77% (5). Inadequate biopsy length has been identified in many, but not all, studies as a key factor in determining the diagnostic yield (sensitivity) of TAB for GCA diagnosis, attributable to "skip lesions" in the artery. Yet there is also a lack of consensus regarding the optimal TAB length. Reasons for these discrepancies may include the lack of standardization of biopsy harvesting, processing techniques and reporting, underlying differences in the TAB diagnostic yield due to differences in TAB referral (17), as well as a variable number of patients already on corticosteroid treatment at the time of biopsy.

In this study we have confirmed that there is a linear relationship between pre-fixation TAB length and the proportion of positive TAB results. Yet there are also practical constraints on the routinely achievable TAB lengths (particularly in females), and the recommended TAB length must balance

the risk of biopsy with the probability of a positive result. Importantly, we identified that a TAB length of at least 15 mm was optimum for the predictive performance of our model, a result which is supported by two prior studies (18, 19). A high proportion of TAB lengths shorter than 15 mm may be characteristic of many studies, given that an overall mean length of 14.1 mm was estimated from a meta-analysis of 49 studies (4), but an increase to a minimum TAB length of 15 mm is realistic and achievable. To assess the potential impact of this, we estimated that a TAB length of at least 15 mm would have led to a positive TAB in an additional 30 patients who otherwise had a missed diagnosis or reduced treatment options, such as access to Tocilizumab which is reserved for biopsy positive cases in Australia.

Improved awareness of the importance of TAB length may not only decrease diagnostic and treatment delay, but may also obviate the need for a contralateral biopsy when there is a negative result, except when there is high index of clinical suspicion (15, 25). There was some evidence of such an improved awareness in our study, as we observed a small increase in biopsy length over the study duration, which has also been reported by some other studies over a longer time-frame (20, 26). We also observed, perhaps surprisingly, that TAB lengths increased with older age which could be consistent with an awareness of the importance of TAB in these patients who have a higher probability of GCA. In contrast, TAB length was shorter in females who also have a higher probability of GCA. This suggests that there may also be some anatomical or aesthetic constraints on TAB length. There is variation in site of TAB. Some surgeons preferring the common superficial temporal artery anterior to the tragus of the ear in favor of the frontal branch of the temporal artery. The difference in yield between these sites was not compared but might be useful to determine in future studies.

The strengths of this study are that it is a large study with all TAB processing and testing performed at a single laboratory which handles approximately 75% of TAB in South Australia. Therefore, it is a representative sample of suspected GCA cases in South Australia, without additional variability in sample processing and reporting. Some limitations include that there was no follow-up on the final clinical diagnosis, and therefore the effect of TAB length on the sensitivity/specificity of TAB for GCA diagnosis could not be evaluated. Further, there was no information on corticosteroid treatment at the time of biopsy, which may have also modified the relationship between TAB length and a positive TAB.

In conclusion, TAB remains a mainstay for a diagnosis of GCA, and TAB length is an important determinant of a positive result. We recommend a minimum pre-fixation length of 15 mm to obtain the maximum diagnostic yield for this procedure, yet approximately half of the biopsies in our study, and likely most published studies, did not meet this criterion. While there are some indications that awareness of the importance of TAB length is increasing amongst vascular or ophthalmologic surgeons, further emphasis is required. Standardization of TAB harvesting, processing techniques and reporting (including length) may also contribute to optimal diagnosis of biopsy-proven GCA.

Data availability statement

Data is not available for privacy reasons. Requests to access the datasets should be directed to CH, catherine.hill@sa.gov.au.

Ethics statement

The studies involving human participants were reviewed and approved by the Central Adelaide Local Health Network Human Research Ethics Committee. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

CR, CH, SLy, JN, and SLe: contribution to study conception and design. CR, JN, KD, SLe, TD, and CH: contribution to data acquisition. CR, JN, SLy, JT, RB, SLe, and CH: contribution to data analysis and interpretation. CR, JN, KD, SLy, JT, RB, TD, SLe, and CH: drafting the manuscript and critical revision and final approval of manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Hunder GG, Bloch DA, Michel BA, Stevens MB, Arend WP, Calabrese LH, et al. The American college of rheumatology 1990 criteria for the classification of giant cell arteritis. *Arthritis Rheum.* (1990) 33:1122–8. doi: 10.1002/art.1780330810

2. Dejaco C, Ramiro S, Duftner C, Besson FL, Bley TA, Blockmans D, et al. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. *Ann Rheum Dis.* (2018) 77:636–43. doi: 10.1136/annrheumdis-2017-212649

3. Stacy RC, Rizzo JF, Cestari DM. Subtleties in the histopathology of giant cell arteritis. *Semin Ophthalmol.* (2011) 26:342–8. doi: 10.3109/08820538.2011.588656

4. Ing EB, Wang DN, Kirubarajan A, Benard-Seguin E, Ma J, Farmer JP, et al. Systematic review of the yield of temporal artery biopsy for suspected giant cell arteritis. *Neuroophthalmology.* (2019) 43:18–25. doi: 10.1080/01658107.2018.1474372

5. Rubenstein E, Maldini C, Gonzalez-Chiappe S, Chevret S, Mahr A. Sensitivity of temporal artery biopsy in the diagnosis of giant cell arteritis: a systematic literature review and meta-analysis. *Rheumatology.* (2020) 59:1011–20. doi: 10.1093/rheumatology/kez385

6. Muratore F, Kermani TA, Crowson CS, Green AB, Salvarani C, Matteson EL, et al. Large-vessel giant cell arteritis: a cohort study. *Rheumatology.* (2015) 54:463–70. doi: 10.1093/rheumatology/keu329

7. Klein RG, Campbell RJ, Hunder GG, Carney JA. Skip lesions in temporal arteritis. *Mayo Clin Proc.* (1976) 51:504–10.

8. Dasgupta B, Borg FA, Hassan N, Alexander L, Barraclough K, Bourke B, et al. BSR and BHPR guidelines for the management of giant cell arteritis. *Rheumatology.* (2010) 49:1594–7. doi: 10.1093/rheumatology/keq039a

9. 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) 68:318–23. doi: 10.1136/ard.2008.088351

10. McMurran AE, Boom SJ. Temporal artery biopsies: do they make the cut? *Scott Med J.* (2015) 60:9–12. doi: 10.1177/0036933014559441

11. Taylor-Gjevre R, Vo M, Shukla D, Resch L. Temporal artery biopsy for giant cell arteritis. *J Rheumatol.* (2005) 32:1279–82.

12. Ypsilantis E, Courtney ED, Chopra N, Karthikesalingam A, Eltayab M, Katsoulas N, et al. Importance of specimen length during temporal artery biopsy. *Br J Surg.* (2011) 98:1556–60. doi: 10.1002/bjs.7595

13. Muratore F, Boiardi L, Cavazza A, Tiengo G, Galli E, Aldigeri R, et al. Association between specimen length and number of sections and diagnostic yield of temporal artery biopsy for giant cell arteritis. *Arthritis Care Res.* (2021) 73:402–8. doi: 10.1002/acr.24393

14. Mahr A, Saba M, Kambouchner M, Polivka M, Baudrimont M, Brocheriou I, et al. Temporal artery biopsy for diagnosing giant cell arteritis: the longer, the better? *Ann Rheum Dis.* (2006) 65:826–8. doi: 10.1136/ard.2005.042770

15. Nordborg E, Nordborg C. Giant cell arteritis: strategies in diagnosis and treatment. *Curr Opin Rheumatol.* (2004) 16:25–30. doi: 10.1097/00002281-200401000-00006

16. Sharma NS, Ooi JL, McGarity BH, Vollmer-Conna U, McCluskey P. The length of superficial temporal artery biopsies. *ANZ J Surg.* (2007) 77:437–9. doi: 10.1111/j.1445-2197.2007.04090.x

17. Goslin BJ, Chung MH. Temporal artery biopsy as a means of diagnosing giant cell arteritis: is there over-utilization? *Am Surg.* (2011) 77:1158–60. doi: 10.1177/000313481107700927

18. Chu R, Foster C, Ali M, Chaba T, Clifford AH, Mahr A, et al. Optimal length and usefulness of temporal artery biopsies in the diagnosis of giant cell arteritis: a 10-year retrospective review of medical records. *Lancet Rheumatol.* (2020) 2:e774–8. doi: 10.1016/S2665-9913(20)30222-8

19. Oh LJ, Wong E, Gill AJ, McCluskey P, Smith JEH. Value of temporal artery biopsy length in diagnosing giant cell arteritis. *ANZ J Surg.* (2018) 88:191–5. doi: 10.1111/ans.13822

20. Aghdam KA, Sanjari MS, Manafi N, Khorramdel S, Alemzadeh SA, Navahi RAA. Temporal artery biopsy for diagnosing giant cell arteritis: a ten-year review. *J Ophthalmic Vis Res.* (2020) 15:201–9.

21. Alnaimat F, Mansour AT, Alduraidi H, Al-Qasem S, Hindi M, Rawashdeh T, et al. Clinical and technical determinants of positive temporal artery biopsy: a retrospective cohort study. *Rheumatol Int.* (2021) 41:2157–66. doi: 10.1007/s00296-021-05028-6

22. Arashvand K. The value of temporal artery biopsy specimen length in the diagnosis of giant cell arteritis. *J Rheumatol* (2006) 33:2363–4; author rely 4.

23. Papadakis M, Kaptanis S, Kokkori-Steinbrecher A, Floros N, Schuster F, Hubner G. Temporal artery biopsy in the diagnosis of giant cell arteritis: bigger is not always better. *Am J Surg.* (2018) 215:647–50.

24. Dunstan E, Lester SL, Rischmueller M, Dodd T, Black R, Ahern M, et al. Epidemiology of biopsy-proven giant cell arteritis in South Australia. *Intern Med J.* (2014) 44:32–9. doi: 10.1111/imj.12293

25. Danesh-Meyer HV, Savino PJ, Eagle RC Jr, Kubis KC, Sergott RC. Low diagnostic yield with second biopsies in suspected giant cell arteritis. *J Neuroophthalmol.* (2000) 20:213–5. doi: 10.1097/00041327-200020030-00011

26. Au CP, Sharma NS, McCluskey P, Ghabrial R. Increase in the length of superficial temporal artery biopsy over 14 years. *Clin Exp Ophthalmol.* (2016) 44:550–4. doi: 10.1111/ceo.12733

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EDITED BY
Andreas P. Diamantopoulos,
Akershus University Hospital, Norway

REVIEWED BY
Roberto Padoan,
University of Padua, Italy
Hubert De Boysson,
Centre Hospitalier Universitaire
de Caen, France

*CORRESPONDENCE
Bayan Al Othman
bayan_alothman@urmc.rochester.edu

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Current developments in the diagnosis and treatment of giant cell arteritis

Denes Szekeres[1] and Bayan Al Othman[2]*

[1]School of Medicine and Dentistry, University of Rochester Medical Center, Rochester, NY, United States, [2]Department of Ophthalmology, University of Rochester Medical Center, Rochester, NY, United States

Giant cell arteritis is the most common vasculitis in adults above 50 years old. The disease is characterized by granulomatous inflammation of medium and large arteries, particularly the temporal artery, and is associated acutely with headache, claudication, and visual disturbances. Diagnosis of the disease is often complicated by its protean presentation and lack of consistently reliable testing. The utility of color doppler ultrasound at the point-of-care and FDG-PET in longitudinal evaluation remain under continued investigation. Novel techniques for risk assessment with Halo scoring and stratification through axillary vessel ultrasound are becoming commonplace. Moreover, the recent introduction of the biologic tocilizumab marks a paradigm shift toward using glucocorticoid-sparing strategies as the primary treatment modality. Notwithstanding these developments, patients continue to have substantial rates of relapse and biologic agents have their own side effect profile. Trials are underway to answer questions about optimal diagnostic modality, regiment choice, and duration.

KEYWORDS

giant cell (temporal) arteritis, color Doppler ultrasonography (CDUS), biologic therapeutics, clinical trials, diagnostics - clinical characteristics

1 Introduction

Large vessel vasculitis (LVV) refers to a spectrum of diseases unified by granulomatous inflammation of the aorta and its major branches. Takayasu arteritis and giant cell arteritis (GCA) are the major entities of LVV, differing in primarily in their age of onset. The focus of this review will be GCA, the most common vasculitis in adults above 50 years old. While patients may present classically with headache, jaw claudication and visual disturbances in the setting of other constitutional symptoms, there is a wide spectrum of disease (1). Disease flares may cause permanent vision loss, cerebral ischemia or aortic aneurysms if not treated promptly with corticosteroids. Often, patients will require other adjunctive therapeutics to prevent relapse or treat steroid-refractory disease. Since the first histological description of GCA in the

early 20th century, (2) there have been numerous developments in elucidating its pathogenesis and optimizing its management. The present paper will review the disease with mention of diagnostic advancements, shifts in treatment strategies, and several landmark trials exploring novel therapeutics.

2 Pathophysiology

The granulomatous inflammation of the medium- and large-sized vessels arising from the aortic arch is mediated by a slew of cellular and humoral immune components (**Figure 1**). The inciting factor for development of GCA is unknown but thought to be virus-related. Resident dendritic cells were shown to be the first immune elements that are activated via their toll like receptors (TLRs) (3). Mature dendritic cells release a variety of chemokines that trigger the recruitment and differentiation of various members of the $CD4^+$ T cell lineage.

The release of IL-1β, IL-6, and IL-23 from dendritic cells induce the differentiation of $CD4^+$ T cells into T-helper 17 (Th17) cells. The Th17 subtype, and their derivative cytokines IL-17, IL-22, and GM-CSF, play a vital role in initiating the pro-inflammatory response. Th17 cells stimulate the hepatic production of acute phase reactants (APRs) and other immune cells such as monocytes (4). The dendritic and Th17 cell pools are also responsible for the downregulation of T regulatory (Treg) cells through IL-6 and IL-17, respectively. The blunting of the typical anti-inflammatory balance is, at least partially, responsible for the chronic nature of GCA (5).

Dendritic cells additionally induce the differentiation of $CD4^+$ T cells into Th1 cells through IL-12 and IL-18. Th1 cells tend to release mediators of chronic inflammation, including interferon gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α). IFN-γ is involved in the activation of vascular smooth muscle cells and the recruitment of monocytes and their differentiation into macrophages. Histiocytes subsequently form the eponymous multinucleated giant cell under the influence of TNF-α (6). Notably, while the Th17 cells appear to be modulated by glucocorticoid therapy, the Th1 subtype remains active in chronic disease (7).

While B cells play a less significant role in the pathogenesis of GCA, there have been implications of B cell pool dysregulation in recently diagnosed patients (8). A 2019 histological examination of 9 aortic biopsies in patients with GCA found adventitial B cell infiltrate organizing into a lymphoid pattern typical of large vessel vasculitides such as Takayasu arteritis (9). Two chemokine axes, CXCL9-CXCR3 and CXCL13-CXCR5, have been implicated in the recruitment and organization of B cells in GCA, though further work should elucidate its role as a therapeutic target (10).

Macrophages were shown to play a key role in intimal hyperplasia and angiogenesis through the release of platelet derived growth factor (PDGF) and matrix metalloproteinases (MMPs) (11–13). Vascular stenosis and thrombosis from intimal hyperplasia is responsible for the jaw claudication and ocular manifestations of GCA. MMPs degrade the media and are responsible for vessel aneurysm. Cytokines, particularly IL-6, remain the backbone of the systemic inflammatory reaction and are responsible for the constitutional signs such as fever, malaise, and myalgias. The culmination of these inflammatory mediators in GCA alludes to the many potential targets for novel steroid-sparing therapy.

3 Clinical presentation

The spectrum of symptoms in patients with GCA are a sequela of vascular occlusion and thus prompt vascular, ophthalmologic, rheumatologic, and neurologic workups. The GCA disease spectrum encompasses three broad phenotypes: Cranial GCA (C-GCA), Large Vessel GCA (LV-GCA), and mixed. C-GCA is associated with the prototypical symptoms of GCA including headache, temporal artery abnormalities and visual disturbances. LV-GCA includes the development of aneurysms or arterial stenoses and presents with limb claudication and aortitis, alongside the traditional symptoms (14). While large vessel involvement occurs in less than half of patients with any GCA, it is associated with increased mortality (15, 16). The mixed phenotype includes features of both C-GCA and LV-GCA and may represent nearly 80% of GCA cases (17).

There appear to be additional associations with polymyalgia rheumatica, another common inflammatory disease with similar epidemiology, pathophysiology, and presentation. A recent meta-analysis of 566 patients found that over 25% of patients with polymyalgia rheumatica (PMR) may present with signs of subclinical GCA, particularly increased aortic uptake in PET scanning (18). Best practice management for these subtypes remains an area of continued investigation (19).

Certain constitutional symptoms are present in most patients with 50% of patients experiencing a low-grade fever, though in some patients the only presenting symptoms may be myalgias. Beyond fever, headache with scalp tenderness, fatigue, facial pain, and weight loss have all been associated with GCA. Notably, one meta-analysis found that the presence of temporal headache did not confer a significantly higher likelihood ratio for diagnosis of GCA. However, other vaso-occlusive signs such as jaw and limb claudication were more sensitive for diagnosis of GCA (20).

Temporal artery abnormalities may present as nodular, tortuous swellings of the vessel with possible loss of pulsation. These findings are secondary to the intimal hyperplasia and sclerosis from chronic inflammation and macrophage-derived PDGF and MMPs (13). A 2021 meta-analysis collected data from 68 studies and approximately 4,000 biopsy-confirmed unique cases of GCA. The authors suggested that any temporal regional abnormality or temporal arterial tenderness

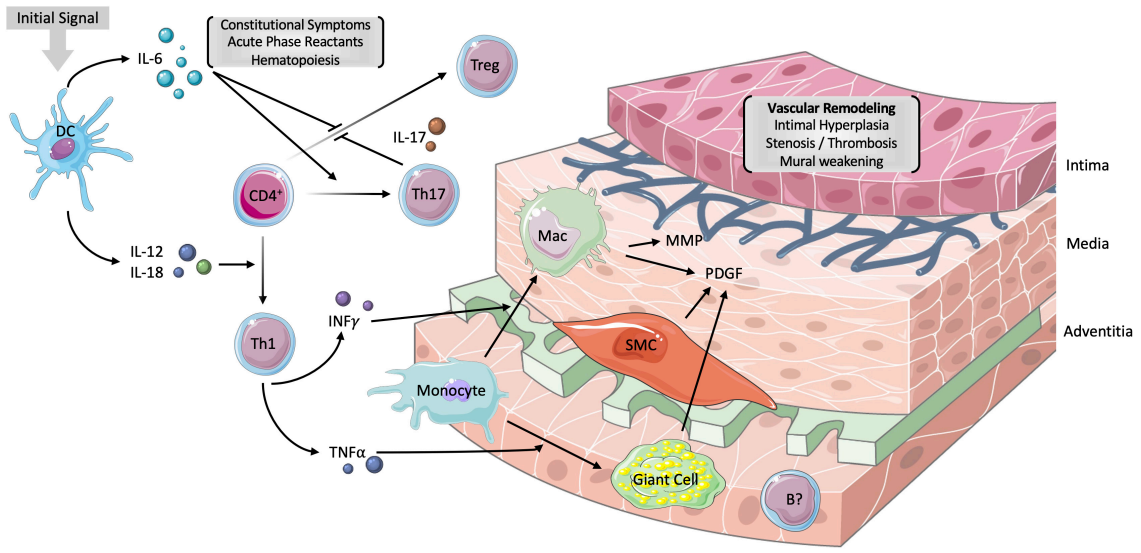

FIGURE 1
Vascular pathogenesis of GCA. The inciting factor for the development of GCA is unknown but though to involve the activation of resident dendritic cells via their toll-like receptors. The subsequent release of interleukin IL-6 and IL-12 promotes the differentiation of $CD4^+$ T-helper cells (Th) into Th17 and Th1 cells, respectively. Th17 cells release IL-17 which is responsible for inhibiting T-regulatory (Treg) cells, stimulating hepatic acute phase reactants (APRs) and monocytes. Th1 cells release mediators of chronic inflammation, including interferon gamma (IFNγ) and tumor necrosis factor alpha (TNFα). While the former stimulates monocyte differentiation into macrophages, the latter influences the formation of multinucleated giant cells. The net of effect of macrophages, smooth muscle cells (SMCs) and giant cells is the release of platelet-derived growth factor (PDGF). PDGF is responsible, in part, for the intimal hyperplasia, stenosis, and thrombosis of large vessels in GCA. Matrix metalloproteinases (MMP) are derived from macrophages and result in the degradation of the tunica media. The resulting vascular remodeling underlies aneurysms in GCA. B cells have no established role in GCA but have been found in the adventitia of arterial biopsies and are implicated in certain chemokine axes. IL-6 is responsible for the constitutional symptoms such as fever and malaise as well as the production of APRs. DC, dendritic cell; $CD4^+$, $CD4^+$ T-helper cell; Mac, macrophages; IL, interleukin. Parts of the figure were drawn by using pictures from Servier Medical Art. Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).

or pulselessness doubled the odds, at minimum, for a positive biopsy (21).

Data from a large population-based cohort found that visual changes occur in around 20% of patients and progressing to vision loss occurs in less than 5% (22). Commonly, patients will report a transient, painless monocular vision loss (i.e., amaurosis fugax), though it may be painful in up to 10% of patients (23). Vision loss in GCA is often secondary to arteritic anterior ischemic optic neuropathy (AAION) due to occlusion of the short posterior ciliary arteries that supply the choroid and optic disk. This phenomenon appears as "chalk white" optic disk edema with possible hemorrhage and cotton-wool spots on fundoscopic examination. Less commonly, GCA-associated vision loss may be due to posterior ischemic optic neuropathy or central retinal artery occlusion. Rarely, patients will present with diplopia due to ischemia of extraocular muscles or visual hallucinations, as described in previous literature (23–25).

3.1 Other associations

GCA symptomology may often be vague and variable. The malaise, headache, fever, and elevated CRP in conjunction with rare reports of dry cough, have generated some diagnostic confusion with COVID-19. Associated diagnostic delay has been suggested to be responsible for increase morbidity from GCA in a single-center fast-track program (26). A 2021 systematic literature review of several cohorts compared the clinical presentation of GCA and COVID-19 and identified key distinguishing features. Jaw claudication and visual loss were rarely reported in COVID-19 cases while lymphopenia appeared nearly exclusively in GCA (27). Interaction of the two disease processes, particularly due to the upregulation of IL-6 and IL-7 in both conditions, has the potential to produce serious adverse outcomes, as described in two case studies with GCA-associated visual loss (28, 29). How, if at all, management is adjusted based on COVID remains an area of investigation.

3.2 Relapse

Relapse during or after glucocorticoid therapy has been reported in over half of patients and up to 21% experience multiple relapses. One study found that relapse appeared independent of glucocorticoid dosage and often appeared while undergoing treatment (30). Other risk factors for relapse are

TABLE 1 1990 ACR Guidelines for GCA.

Score	Criterion
1	Age at disease onset greater than 50 years
1	New headache
1	Temporal artery abnormality ◇
1	Erythrocyte sedimentation rate greater than 50 mm/hr
1	Abnormal temporal artery biopsy

A patient is deemed to have GCA and are recommended to have a TAB if they meet three or more of these criteria.
◇Including tenderness to palpation or decreased pulsation.

TABLE 2 rACR Guidelines for GCA.

Score	
	Entry Criterion
–	Age at disease onset greater than 50 years
–	Absence of exclusion criteria◇
	Domain I
1	New onset localized headache
1	Sudden onset of visual disturbances
2	Polymyalgia Rheumatica (PMR)
1	Jaw Claudication
2	Abnormal temporal artery on physical exam
	Domain II
1	Unexplained fever or anemia
1	ESR greater than 50 mm/hr
2	Compatible pathology▽ on biopsy

Expanded set of criteria across two domains of presentation. Patients with three points out of the eleven total are diagnosed with GCA.
◇Including tenderness to palpation or decreased pulsation.
▽Fibrinoid necrosis with perivascular leukocyte invasion and granulomas.

less well established, with a recent study showing that LV-GCA, a negative TAB, primarily musculoskeletal symptoms, and female gender were all associated with an increased risk (31). Another recent trial found that higher platelet count and a glucocorticoid-induced transcript 1 polymorphism reduced the risk of relapse (NCT01400464) (32). While relapse symptoms are often milder – reporting as being headaches, PMR-like symptoms, or claudication – patients would nevertheless benefit from treatments with sustained remission (33, 34).

4 Diagnostics

Even before obtaining confirmatory diagnostic testing, immediate treatment with corticosteroids and tocilizumab is recommended in cases with high suspicion of GCA. Criteria for the diagnosis of GCA were originally set forth in 1990 by the American College of Rheumatology (ACR; **Table 1**). Accordingly, patients are deemed to have GCA and are recommended TAB if they meet three or more of the five criteria, with a sensitivity of 93.5% and specificity 91.2% (35). One major pitfall of the criteria arises in cases of very low or high pretest probability; for example, if a patient presents with a new headache over the age of 50 with elevated ESR, they are recommended a TAB. Whereas these protean symptoms may be sequelae of malignancy, infection, or other autoimmune conditions, rather than GCA. A recent paper proposed a revised set of criteria (rACR) to avoid temporal artery biopsy in cases such as above or in those with cardinal symptomology. The rACR stratifies criteria into two domains, one encompassing the cardinal and the other the protean signs and symptoms, for a total of nine points (**Table 2**). In a review of the criteria 100% of patients scoring five or more had a positive biopsy and thus could possibly avoid biopsy. A score of three or more detected 91% of positive cases, whether or not it is acceptable to miss one to two cases to avoid biopsy is debated (36, 37).

The two main governing bodies, the ACR and EULAR, recently released joint guidelines for the classification of GCA (**Table 3**). These guidelines are applied after the diagnosis of a medium- or large-vessel vasculitis is established to further classify the presentation as GCA. Importantly, these are not aimed to be used as initial diagnostic criteria. Analysis of the 2022 criteria found a sensitivity of 87% and specificity of 95%, with superior sensitivity when compared to the 1990 ACR criteria (38).

4.1 Temporal artery biopsy

TAB should be performed as soon as possible after beginning glucocorticoids and the ACR continues to recommend a long segment (>1 cm), unilateral biopsy in conjunction with clinical evaluation as the gold-standard for diagnosis. A retrospective cohort showed that biopsy results were positive in 78% of clinically-diagnosed GCA that started treatment within two weeks of TAB. A delay of over four weeks showed TAB-positivity in only 40% of patients, suggesting normalization of histologic findings (39). However, due to the small sample size of 78 patients with only five receiving TAB after four weeks, extrapolation to the broader clinical setting may be less robust. Nonetheless, a meta-analysis of 3,092 patients revealed that TAB had a pooled 77% sensitivity with a decreasing trend in positive biopsies, on par with other diagnostic testing (40).

Examination of temporal artery biopsies with hematoxylin and eosin staining typically shows panarterial lymphocytic infiltrates with granulomas. The evaluation may also reveal hyperplasia and fragmentation of the elastic laminae with minimal neutrophil invasion. Elastic van Gieson may reveal disruption of the internal elastic lamina and, while used for repeat biopsies, is not routinely recommended by the ACR

TABLE 3 2022 ACR/EULAR Classification Guidelines for GCA.

Score	
Absolute requirement	
–	Age at disease onset greater than 50 years
Additional clinical criteria	
2	Morning stiffness in shoulders or neck
3	Sudden onset visual loss
2	Jaw or tongue claudication
2	New temporal headache
2	Scalp tenderness
2	Temporal artery abnormality ◇
Laboratory, Imaging, and Biopsy Criteria	
3	Maximum ESR greater than 50 mm/hr or maximum CRP greater than 10 mg/L
5	Positive temporal artery biopsy or positive halo sign on temporal artery ultrasound
2	Bilateral axillary involvement ▽
2	FDG-PET activity throughout aorta

These criteria classify medium- or large-vessel vasculitis as GCA after excluding other etiologies. A sum of scores greater than or equal to 6 is deemed positive for GCA.
◇Including tenderness to palpation, cord-like appearance, or decreased pulsation.
▽Angiography showing luminal stenosis, increased uptake on FDG-PET, halo sign on ultrasound.

(41). Skip lesions have been reported in roughly 10% of cases and raise concern for missed diagnoses, hence, the whole clinical picture and additional diagnostics remain important for thorough workup (42).

There are plethora patterns of GCA beyond the classic histological changes described above, which underlies the variability in disease presentation (43). One study proposed a model of sequential angioinvasion, beginning with adventitial involvement and ending with a panarterial inflammatory infiltrate. However, aside from an association of severe cranial symptoms with a panarterial pattern, the authors found few prognostic indicators based on histology alone (42).

4.2 Color Doppler ultrasound

Color Doppler Ultrasound (CDUS) is an ultrasonography technique that assesses directionality of blood flow. CDUS was first shown to be able to diagnose GCA in certain high pre-test probability cases in 1997 (44). Of particular importance is the ability to simultaneously image other cranial rami and large arteries including the axillary and subclavian, without added invasive testing. A meta-analysis of 43 individual studies found that CDUS has a specificity of 96% and sensitivity of 77% for GCA (45). The evaluation of ultrasound's role in patients suspected of having extracranial and cranial giant cell arteritis or EUREKA study was a recent multicenter cohort study. Researchers demonstrated comparable specificities and sensitivities to prior work and showed that positive CDUS findings independently conferred a greater odds ratio for GCA diagnosis at six months than TAB alone (46). A separate multicenter prospective cohort study, the role of ultrasound compared to biopsy of temporal arteries in the diagnosis and treatment of giant cell arteritis, or TABUL, suggested that CDUS has superior sensitivity though inferior specificity compared to TAB (47). Collectively, these findings suggest CDUS may soon be considered the most appropriate first line test.

The prototypical finding in GCA is a dilated superficial temporal artery with a non-compressible, hypoechoic "halo" in the vessel wall, reflecting panarterial inflammation, thickening, and edema (44, 48). However, the incompressible halo sign is not pathognomonic for GCA. Many ultrasonographic features are shared among other ANCA-associated vasculitides, amyloidosis, and atherosclerosis, often complicating diagnosis in uncertain cases (49). Concerns were raised regarding poor inter-rater reliability described in one study (47). The implementation of recent training programs has shown good reliability with up to 96% interobserver agreement (48, 50, 51).

The prognostic and longitudinal utility of CDUS is still under investigation. The Halo Score is a recent development by *van der Geest* and colleagues and is predicated on the counting of halos in several temporal and axillary artery segments. While the sensitivity and specificity of this test alone was not superior to standard US workup, a high Halo Scores accurately identified patients at considerable risk for vision loss (52). Future work may explore the possibility of tailoring patients' glucocorticoid dosing schedule based on such scoring.

Joint CDUS and TAB "fast-track pathways" are increasingly used by institutions (53–56). These programs employ a multidisciplinary team and structured algorithms to rapidly evaluate, diagnose, and define treatments for patients with suspected GCA. One study found significant reduction in vision loss due to faster time to diagnosis and initiation of treatment but no change in rates of relapse (55). The TABUL study demonstrated that ultrasound alone may provide comparable diagnostic accuracy with a significant reduction in cost and a theoretical 43% reduction in biopsies. Notably, the authors found that both ultrasonographers and pathologists had moderate interrater agreement (47). How, and if for all patients, fast-track pathways will continue utilizing TAB as a diagnostic standard is still under debate.

The use of CDUS to monitor disease progression is less well-documented. A 2018 systematic review found that the halo sign resolves in most patients undergoing adequate treatment, though no other reliable prognostic features were identified (45). The optimal use of CDUS remains a subject of investigation with recent literature examining the role of axillary (57, 58) and extended ultrasonographic evaluation in prognosis and disease monitoring (59, 60). Results of a recent study suggest that

limited CDUS of the axillary arteries misses 4% of patients with LV-GCA identified by an extended exam (including carotid, vertebral, subclavian, and axillary arteries). Furthermore, in this study population, 9% of patients with LV-GCA had only vertebral artery involvement (59). Such extended examination requires advanced equipment and training that may ultimately be worthwhile for monitoring disease progression without the need for contrast agents used in other modalities. The advent of higher resolution probes may impact specificity of CDUS and its integration into practice is currently under investigation (NCT04204512).

4.3 FDG-Positron emission tomography

2-[Fluorine-18]-fluoro-2-deoxyglucose positron emission tomography (FDG-PET) is an imaging technique grounded in measuring metabolic activity and traditionally used for the diagnosis, staging and monitoring of malignancies. The modality has been shown to be applicable for hypermetabolic lesions such as GCA and other chronic inflammatory disorders with active cellular infiltrate (61). However, it is not considered a first-line diagnostic modality due its cost and radiation exposure. FDG-PET was first employed in tracking the involvement of large arteries in LV-GCA. Recent advancements in imaging technology permit the spatial resolution of the smaller cranial vessel involvement in C-GCA and distinguish lesions from the high background cranial uptake of FDG (62). Results from the Giant Cell Arteritis and PET Scan (GAPS) study showed that FDG-PET of the head and chest has a negative predicative value of 98%, though up to 20% of patients have additional incidental findings (NCT02771483) (63). A 2022 trial found that the combined use of cranial and extracranial FDG-PET decreased specificity and positive predictive value but increased sensitivity and negative predictive value in diagnosing GCA (NCT05246540) (64). The use of combined FDG-PET and magnetic resonance imaging (MRI) with angiography (MRA) has also been explored. While MRI alone can resolve GCA-associated intimal hyperplasia and other inflammatory changes (65), combined FDG-PET/MRI provides an additional lens to evaluate the underlying biochemical mechanisms (66, 67). How this will change standard imaging is under evaluation and it's use as the sole diagnostic test is under scrutiny (NCT04204876 & NCT05000138). Considering the cost of these modalities, FDG-PET may be less practical than point-of-care CDUS.

The role of FDG-PET in prognosis and longitudinal evaluation is similarly unclear. FDG uptake did not appear to distinguish patients with active disease and those in remission (68) and appeared to normalize within three days of beginning glucocorticoid therapy (69). In LV-GCA, increased aortic FDG uptake was shown to be associated with an increased risk of thoracic aneurysm (70, 71). To date, no other correlations with disease patterns have been elucidated and there remains a paucity of research on the clinical impact of FDG-PET results.

The focus of current research is the discovery of novel radiotracers that may have improved specificity for GCA. A recent trial was started comparing the use of Ga-DOTATATE to FDG for the detection of inflammation and its potential to correlate with disease activity in patients receiving glucocorticoids (NCT03812302). The use of a somatostatin receptor tracer is also under investigation (NCT04071691). While many other tracers are currently in trial for their use in monitoring cancers, T cell- (72) and macrophage-specific (73, 74) tracers have been shown to identify areas of vascular inflammation and could be extrapolated to GCA. These studies are reviewed in detail elsewhere (75).

4.4 Magnetic resonance imaging

MRI is a high-resolution imaging modality that has been shown to be effective in evaluating inflammation of cranial vessels. Imaging may show evidence of luminal stenosis, vessel dilatation or aneurysms. Compared to TAB, MRA was 93% sensitive and 81% specific for GCA (45). The ACR recommends the use of MRA for the diagnosis of GCA if biopsy or CDUS is inconclusive (41). Interestingly, a 2022 study demonstrated that while CDUS, MRA, and retinal angiography were independently accurate, a combination of MRA followed by CDUS if inconclusive was 100% sensitive, specific, and accurate (76). These findings support EULAR guidelines which recommend a multi-modality diagnostic approach. Additional studies are needed to compare FDG-PET with MRA.

Disease monitoring after initial presentation is also recommended based on institutional availability to evaluate the extent of large vessel aneurysms and stenoses. Imaging frequency and modality should be determined by joint patient physician decision-making. Compared to CDUS, a small study found that MRA did not have significant differences in sensitivity and specificity in the diagnosis of GCA, when compared to TAB (77). A more recent cross-sectional study found that CDUS was more sensitive in detecting vasculitic changes in large vessels compared to MRA (78). Given the higher cost of MRA and the exposure to contrast, CDUS is often a more appropriate test.

4.5 Conventional angiography

Computed tomography angiography (CTA) has been used in the historical evaluation of large vessel involvement in GCA and often shows wall thickening with a double ring of contrast enhancement. A small case-control study showed that CTA was able to resolve superficial temporal artery abnormalities such as perivascular contrast enhancement and blurring of vessel walls (79). Several studies (80, 81) suggest that PET/CT provides

superior sensitivity over CTA alone. This is reflected in the EULAR guidelines, which do not routinely recommend that the diagnosis of GCA or evaluation of LVV hinge on CTA (82).

4.6 Laboratory markers

The inflammatory milieu in generalized inflammation stimulates the hepatocellular production of C-reactive protein (CRP). While CRP is a direct marker of inflammation, erythrocyte sedimentation rate (ESR) is a surrogate marker, reflecting the increase in fibrinogen that may occur secondary to many conditions. Measurement of these markers is standard in the workup of GCA, and both are often markedly elevated in patients with acute disease. ESR above 100 mm/hr was found to be associated with a 3-fold increase in likelihood of GCA, whereas ESR below 40 mm/hr or a CRP below 2.5 mg/dl nearly halved the likelihood of GCA (20).

4.7 Diagnostic guidelines

Both the ACR and EULAR have recently updated their guidelines to reflect the advancements in diagnostic imaging. While largely similar, there are some differences in the diagnostic guidelines set forth by the ACR and the EULAR. Notably, the ACR guidelines continue to endorse a TAB over temporal ultrasound owing largely to differences in ultrasonographic training. While they recommend adjunctive large vessel imaging after confirmation by biopsy, angiographic imaging alone is not deemed sufficient for initial diagnosis (41). Contrarily, the EULAR cite a strong level of evidence for diagnosis without biopsy in cases of positive cranial MRA or temporal and axillary ultrasound (82). Longitudinal imaging, while evidenced to have value in monitoring structural damage, is not routinely recommended by the EULAR. Instead, personal preference and cost-benefit analysis should drive clinical decision-making when evaluating disease flares. The ACR recommends that some form of longitudinal clinical monitoring be done, whether it be clinical examination, laboratory evaluation or imaging. In light of the recent 2022 joint ACR/EULAR classification criteria, unified diagnostic guidelines may be on the horizon.

5 Management

5.1 Glucocorticoids

Glucocorticoids have been vital for the acute and chronic treatment of GCA. Through several mechanisms, including inhibition of the Th17 cell pool, glucocorticoids modulate inflammation and effectively reduce the risk of vision loss. Oral glucocorticoids are often initiated at 1 mg/kg/day with higher dosing for patients with severe ophthalmologic symptoms. The British Society of Rheumatology (BSR) recommends pulsed intravenous (IV) administration of up to five days of 1,000 mg methylprednisolone for patients with high-risk features (83). However there are no randomized controlled trials (RCTs) comparing outcomes of either route, thus clinical decision-making is largely consensus-based (84). The side effect profile of IV glucocorticoids, especially in the elderly populations where GCA is prevalent, should also be taken into consideration when selecting initial treatment.

After initiation, glucocorticoids are generally tapered over the course of a year, although there are differences in published guidelines. In the United States tapering is often six to eight months while the EULAR recommends 18 to 24 months of tapering. A European trial is currently underway comparing rates of remission and side effects for 28- and 52-week tapering regiments (NCT04012905).

5.2 Glucocorticoid-sparing therapies

Patients will often restart courses of glucocorticoids to manage flares, substantially increasing their cumulative exposure. While longer regiments effectively reduce serious GCA-related adverse events, repeated glucocorticoid therapy harbors its own set of serious side effects. Often cited side effects of glucocorticoids include newly diagnosed hypertension, diabetes mellitus, as well as osteonecrosis, increased rates of infections, and cataracts. One case-control study in patients with GCA found that higher cumulative dose of glucocorticoids (30 versus 5 mg/day) was associated with a nearly five-fold increased risk of diabetes mellitus, a two-fold increased risk of osteoporosis and two-fold increased risk in all-cause mortality (85). A larger study based on data from US and UK databases concluded that for each gram of cumulative glucocorticoid exposure, there is a three to eight percent increase in risk of any steroid-related adverse event (86).

Diverse classes of adjunctive therapies have been explored since the initial treatment of GCA with glucocorticoid monotherapy decades years ago (**Table 4**). Many of these therapeutics are currently under laboratory investigation and, to date, methotrexate and tocilizumab are the only FDA-approved treatments in the United States. Guidelines for treatment of the initial disease and subsequent flares are shifting toward prioritizing the newly licensed glucocorticoid-sparing therapy tocilizumab. The follow sections review the noteworthy investigational drugs by their therapeutic class.

5.2.1 Non-biologic adjuncts

5.2.1.1 Methotrexate

Methotrexate is a dihydrofolate reductase anti-metabolite used to treat a variety of malignancies due to its antagonism

TABLE 4 Clinical trials for GCA treatment.

Pathway	Drug target	Agent	Class	Trials
Cytokine signaling				
	IL-1	Anakinra	Recombinant IL-1R antagonist	NCT02902731
	IL-6	Tocilizumab	mAb	NCT01791153, NCT03202368, NCT04239196, NCT03745586, NCT05479448, and NCT05045001
	IL-6	Sirukumab	mAb	NCT02531633
	IL-6	Sarilumab	mAb	NCT03600805
	IL-17	Secukinumab	mAb	NCT03765788, NCT05380453, and NCT04930094
	IL-12/IL-23	Ustekinumab	mAb	NCT03711448
	IL-23	Guselkumab	mAb	NCT04633447
	TNFα	Infliximab	mAb	NCT00076726 and NCT05168475
	TNFα	Etanercept	mAb	NCT00524381 and NCT05168475
	TNFα	Adalimumab	mAb	NCT00305539 and NCT05168475
	GM-CSFRα	Mavrilimumab	mAb	NCT03827018
JAK-STAT signaling				
	JAK1/JAK2	Barcitinib	Small molecule	NCT03026504
	JAK1	Upadacitinib	Small molecule	NCT03725202
T-lymphocyte				
	CTLA4 Analog	Abatacept	Selective costimulatory modulator	NCT04474847

Multiple agents have been explored for the treatment of GCA, with particular interest in the cytokine signaling pathways. Drug targets, classes and respective trials are reviewed. IL, interleukin; TNF, tumor necrosis factor; GM-CSF, granulocyte-macrophage colony stimulating factor; JAK-STAT, janus kinase signal transducer and activator of transcription; CTLA, cytotoxic T-lymphocyte-associated protein; mAb, monoclonal antibody.

of DNA synthesis. Its mechanism in treating autoimmune disorders involves inhibiting the breakdown of adenosine and preventing the activation of T- and B-cells. Methotrexate is the most common non-biologic agent used in addition to glucocorticoids for the management of GCA (87). To date, only three RCTs have been performed with results showing either no difference in rates of relapse (88, 89) or reduction in relapse from 84 to 45% (90). A pooled meta-analysis suggested a 35% reduction in risk of first relapse with significant reduction in total glucocorticoid exposure versus placebo. Whether or not the glucocorticoid-sparing effect of methotrexate outweighs it side effect profile remains unclear from this study (91).

The ACR currently recommends the use of methotrexate based on clinician experience and patient preference (41). How methotrexate will continue to play a role in GCA management is under debate, principally due to the marked efficacy of tocilizumab (92). One advantage of methotrexate is that it is a small molecule chemical and trends significantly cheaper than contemporary biologics. A 2020 RCT is evaluating efficacy of a 12-month treatment of methotrexate versus tocilizumab in 200 patients (NCT03892785). The authors hypothesize that rates of remission will be comparable, resulting in superior cost efficiency. Other non-biologic adjuncts such as azathioprine (93), cyclosporine A (94), and dapsone (95) have been studied but yielded, at most, modest results with strikingly poor side effect profiles.

5.2.1.2 Leflunomide

Leflunomide, with its active metabolite teriflunomide, inhibits dihydroorotate dehydrogenase, a mitochondrial enzyme involved in pyrimidine synthesis. It has been shown as an effective agent in RA, Takayasu arteritis, and PMR (96, 97). Its use in clinical practice is based on results from smaller case reports and open-label studies. Several case series' showed efficacy and good tolerability with steroid-sparing effect in patients with GCA (98, 99). A 2018 observational study demonstrated significant reduction in relapse compared to the glucocorticoid group with a significantly lower cumulative steroid dose (100). Compared to methotrexate, leflunomide appeared to induce remission earlier, particularly in patients requiring higher doses of prednisolone initially (101). To date, there have been no randomized controlled trials comparing leflunomide with standard therapies.

5.2.2 Interleukin pathway inhibitors

5.2.2.1 Interleukin-1

Anakinra, an IL-1 receptor antagonist, showed efficacy in a case series of six patients. Notably, the authors found disappearance of aortitis in one patient and reduction in FDG vascular uptake in three. Four patients achieved steroid-free remission by median 56 months (102). Though the results appear promising, data from an ongoing trial, the Giant Cell

Arteritis and Anakinra Trial (GiAnT), may clarify its efficiency compared to placebo (NCT02902731).

5.2.2.2 Interleukin-6

IL-6 is the predominant cytokine in the pathogenesis of and was found to be consistently elevated in GCA. Tocilizumab, sold under the trade name Actemra®, is a humanized anti-IL-6 receptor monoclonal antibody first used for the treatment of multicentric Castleman disease in 2009 (103). The Giant-Cell Arteritis Actemra (GiACTA) trial is a phase 3 RCT that showed a weekly or biweekly dose of 162 mg tocilizumab with prednisone provided superior rates of remission and longer flare-free intervals than patients solely on prednisone. Adverse events occurred in about 15% of patients receiving tocilizumab but over 22% of patients on placebo and prednisone taper (104). Even with promising results from trials, up to 40% of patients relapsed after cessation of treatment with tocilizumab. Newer research appears to suggest that long-term therapy with tocilizumab may be appropriate. The incidence of adverse events is comparable between treatment regiments greater than or less than a year, with clinical improvement in 90-100% of patients by 24 months (105, 106). Both EULAR (107) and the 2021 ACR (41) guidelines have shifted to recommend tocilizumab with a glucocorticoid taper for both the initial treatment of GCA and management of subsequent flares. Studies of different dosing schedules and routes (108) as well as long-term safety profiles (NCT03202368) are currently underway.

IL-6 is key player in the healthy immune response against infection and blockade of this system is responsible for the increased risk of infection with use of tocilizumab (10% patients per year) (105). As with other immune modulating agents, screening for tuberculosis is recommended prior to beginning treatment. Tocilizumab was also shown to increase the risk for bowel perforation and has been documented to increase lipids in some patients. Trimonthly laboratory monitoring for neutropenia (occurring in about 4% of patients), thrombocytopenia, and hyperlipidemia as well as liver function testing is recommended during treatment.

Sirukumab is another humanized anti-IL-6 monoclonal antibody that entered phase three trial in 2015 (NCT02531633). While results are limited due to early study termination by the sponsoring agency, sirukumab with a prednisone taper was found to reduce number of flares compared to placebo with taper. There were no reports of bowel perforation, but the rates of infection and laboratory abnormalities were consistent with those found in the tocilizumab trial. A related biologic, sarilumab, was under investigation until its suspension in April 2020 due to COVID-19 (NCT03600805).

5.2.2.3 Interleukin-17

IL-17 from Th17 cells is responsible for part of the GCA inflammatory response. While glucocorticoids have already been shown to inhibit the Th17 axis, targeting with biologics may provide additional benefits. Secukinumab is a humanized anti-IL-17A monoclonal IgG antibody, sold under the brand name Cosentyx®, that is currently FDA-approved for the treatment of plaque psoriasis. A phase two trial showed efficacy and an acceptable safety profile of secukinumab versus placebo (NCT03765788). Two recent phase 3 trials are underway and will compare the use of secukinumab with a prednisone taper versus a placebo with taper (NCT05380453 & NCT04930094).

5.2.2.4 Interleukin-12 & Interleukin-23

The IL-12 and IL-23 pathways are the targets for the monoclonal antibody ustekinumab, which may modulate the Th1 and Th17 response simultaneously. A smaller study found that ustekinumab induced complete remission and successfully lowered the total glucocorticoid dose for 14 patients (109). A follow-up open-label study of 13 patients showed poor outcomes with very high rates of relapse (110). In light of these mixed findings, a newer phase two open-label study might better show the efficacy of ustekinumab (NCT03711448). Janssen Pharmaceuticals is currently comparing the use of guselkumab, an IL-23 specific receptor antagonist against placebo in 60 patients (NCT04633447).

5.2.3 T-Llymphocyte modulators

T cell activation requires a CD28-mediated costimulatory signal from antigen presenting cells (APCs). Several trials have explored blocking T cell activation with abatacept, a biologic CTLA4 analog that binds B7 protein on APCs. The first placebo-controlled study showed longer duration of remission but had similar rates of adverse effects compared to prednisone alone (111). Its clinical use is still under investigation with a phase three trial currently underway (NCT04474847). Notably, there was a recent 28-patient study directly comparing the efficacy of abatacept against tocilizumab. In the study cohort, tocilizumab appeared to have superior rates of remission and reduced the cumulative dose of steroids compared to abatacept (112).

5.2.4 TNFα inhibitors

TNFα has been identified in the arteries of patients with GCA. Single case studies and case series' have shown some promise in treatment of GCA (113–116). However, RCTs of infliximab (117), etanercept (118), and adalimumab (119) did not appear to significantly improve outcomes versus placebo and the risk for infections were noticeably higher.

5.2.5 JAK/STAT pathway inhibitors

The Janus Kinase (JAK) and signal transduction activator of transcription (STAT) pathway induces DNA transcription from extracellular ligands such as cytokines. Both Th1 and Th17 have been linked to STAT proteins and thus the JAK/STAT

pathway is thought to play a role in the inflammation of large-vessel vasculitides (120). Indeed, mouse models of vasculitis have shown that inhibition of the JAK/STAT pathway may blunt the production of inflammatory mediators and thus is a feasible target for therapeutics (121).

Baricitinib, sold under the trade name Olumiant®, is a small molecule inhibitor of JAK1 and JAK2 first licensed for the treatment of TNF antagonist-resistant rheumatoid arthritis in 2018. In 2022 it was also licensed for the treatment of alopecia areata and COVID-19. Recently published results from a pilot study of baricitinib (NCT03026504) showed good tolerability and durable glucocorticoid-free remission in 13 of 15 patients (122). Upadacitinib (Rinvoq®), another small molecule inhibitor approved for the treatment of rheumatoid arthritis, is currently under investigation for its use in GCA (NCT03725202).

Despite promising rates of remission, JAK/STAT inhibitors carry an increased risk of infection. As with other immunomodulating therapies, further research and cost-benefit analyses need to be done before its role in the treatment of GCA is solidified.

5.2.6 GM-CSFRα inhibitors

GM-CSF was identified as a key component in the pathogenesis of GCA. Mavrilimumab, a humanized monoclonal antibody that targets the GM-CSF Receptor alpha chain, is a therapeutic agent that was first investigated as a treatment for rheumatoid arthritis in 2011 (123). A recent phase 2 trial showed lower rates of remission and longer time to flares compared to glucocorticoid taper in 42 patients (NCT03827018). While the study reported no serious adverse effects, further work needs to be done to assess long-term efficacy and compare it to tocilizumab and other investigational therapeutics (124).

5.3 Surgical interventions

Surgical interventions in GCA are primarily aimed at ameliorating vascular injuries to the aorta and its major branches. Aside from urgent intervention in cases of dissection or ischemia, the ACR recommends elective surgeries based on patient preference, healthcare team consensus, and during disease remission (41). Vessel stenosis can occur at any time during the disease course, with cases of critical limb ischemia requiring venous bypass grafting or endovascular repair (125, 126). Commonly, the bypassed or repaired vessel may fail either from anastomotic aneurysm or re-occlusion. A recent case series also demonstrated successful endovascular repair of intracranial vessels in patients with tocilizumab-resistant disease and stroke (127). Endovascular repair will likely continue to evolve and play a larger role in cases of GCA with severe angiopathy (128).

6 Discussion

Giant cell arteritis is a granulomatous inflammation of medium and large arteries and is the most common vasculitis in older adults. While it remains a diagnostic challenge, the use of ultrasound has now complemented the traditional temporal artery biopsy as standard workup, though supplementary testing including FDG-PET and MRI are used in certain scenarios. Advancements in diagnostics and the development of streamlined programs have benefited countless patients by reducing time to treatment and improving disease monitoring. Several trials continue to investigate the role of these modalities. One study is currently validating a diagnostic CDUS algorithm and is pending results (NCT02703922). One aims to answer how the diagnostic accuracy of CDUS and FDG-PET change with the onset of treatment (NCT03765424). Another prospective study is directly comparing the clinical use of common diagnostic modalities in GCA diagnosis (NCT05248906). Certainly, with new evidence, more concrete diagnostic algorithms will be implemented.

While there is much research underway for novel agents, there remains a debate about best practice with current standards of treatment. Does time of glucocorticoid taper impact rates of remission and risk of side effects? How do parameters for glucocorticoid taper change with the use of tocilizumab? Does tocilizumab benefit from glucocorticoid administration or is monotherapy sufficient? Does tocilizumab in combination with glucocorticoids reduce risk of AION (NCT04239196)? Where does methotrexate enter the equation and is this antiquated drug still relevant for treatment? Results from several trials in the coming years will hopefully answer some of these questions. The GCA treatment with ultra-short GC and tocilizumab (GUSTO) trial (NCT03745586) showed that a three-day course of high dose glucocorticoids had adequate rates of remission in 13 of 18 patients, comparable to the standard 24-week taper course (129). Another 30-patient open-label trial showed that 12 months of tocilizumab with initial two months prednisone taper was able to induce remission in 77% of patients by 12 months (130). Where along this spectrum is the optimum treatment and can we predict which patients will respond to glucocorticoids or tocilizumab (NCT05479448 & NCT05045001)?

Tocilizumab has shown promise in improving remission and glucocorticoid-associated complications, but the therapy is expensive, confounds common biomarkers for monitoring, and 50% may relapse after cessation of treatment. In the coming years, head-to-head comparisons of efficacy and safety between these anti-interleukin therapies may change best practice guidelines. Already, a RCT comparing the efficacy of the biologics rituximab, infliximab, and tocilizumab using a crossover design is underway in the United Kingdom (NCT05168475). The study is enrolling a broad patient population with diagnoses of any non-ANCA-associated

vasculitides including polyarteritis nodosa, Takayasu arteritis, and GCA, among others. While it is the first trial to date directly comparing several biologic agents, the number of patients with GCA may be limited, lessening the power of the study and its extrapolation to GCA specifically.

Considering all these advancements GCA remains a chronic disease, patient choice and quality of life should still drive treatment decisions. Is there any way to determine who is at risk (NCT01241305 & NCT02967068) and are there any preventative measures that can improve patient outcomes? For those already undergoing treatment, can we give hydrocortisone (NCT042391960) or other 'rescue' therapies to improve quality of life?

Author contributions

BA conceived the idea and scope of the review, reviewed and approved the manuscript. DS performed the literature review and wrote the manuscript. Both authors agreed to be accountable for the content of the work and contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Salvarani C, Pipitone N, Versari A, Hunder G. Clinical features of polymyalgia rheumatica and giant cell arteritis. *Nat Rev Rheumatol.* (2012) 8:509–21. doi: 10.1038/nrrheum.2012.97

2. Horton B, Magath T, Brown G. Arteritis of the temporal vessels: a previously undescribed form. *Arch Intern Med.* (1934) 53:400–9. doi: 10.1001/archinte.1934.00160090077007

3. Ma-Krupa W, Jeon M, Spoerl S, Tedder T, Goronzy J, Weyand C. Activation of arterial wall dendritic cells and breakdown of self-tolerance in giant cell arteritis. *J Exp Med.* (2004) 199:173–83. doi: 10.1084/jem.20030850

4. Tesmer L, Lundy S, Sarkar S, Fox D. Th17 cells in human disease. *Immunol Rev.* (2008) 223:87–113. doi: 10.1111/j.1600-065X.2008.00628.x

5. Adriawan I, Atschekzei F, Dittrich-Breiholz O, Garantziotis P, Hirsch S, Risser L, et al. Novel aspects of regulatory T cell dysfunction as a therapeutic target in giant cell arteritis. *Ann Rheum Dis.* (2021) 81:124–31. doi: 10.1136/annrheumdis-2021-220955

6. Weyand C, Goronzy J. Immune mechanisms in medium and large-vessel vasculitis. *Nat Rev Rheumatol.* (2013) 9:731–40. doi: 10.1038/nrrheum.2013.161

7. Jiusheng D, Younge B, Olshen R, Goronzy J, Weyand C. Th17 and Th1 T-cell responses in giant cell arteritis. *Circulation.* (2010) 121:906–15. doi: 10.1161/CIRCULATIONAHA.109.872903

8. van der Geest K, Abdulahad W, Chalan P, Rutgers A, Horst G, Huitema M, et al. Disturbed B cell homeostasis in newly diagnosed giant cell arteritis and polymyalgia rheumatica. *Arthritis Rheumatol.* (2014) 66:1927–38. doi: 10.1002/art.38625

9. Graver J, Boots A, Haacke E, Diepstra A, Brouwer E, Sandovici M. Massive B-cell infiltration and organization into artery tertiary lymphoid organs in the aorta of large vessel giant cell arteritis. *Front Immunol.* (2019) 10:83. doi: 10.3389/fimmu.2019.00083

10. Graver J, Abdulahad W, van der Geest K, Heeringa P, Boots A, Brouwer E, et al. Association of the CXCL9-CXCR3 and CXCL13-CXCR5 axes with B-cell trafficking in giant cell arteritis and polymyalgia rheumatica. *J Autoimmun.* (2021) 123:102684. doi: 10.1016/j.jaut.2021.102684

11. Kaiser M, Weyand C, Björnsson J, Goronzy J. Platelet-derived growth factor, intimal hyperplasia, and ischemic complications in giant cell arteritis. *Arthritis Rheum.* (1998) 41:623–33. doi: 10.1002/1529-0131(199804)41:43.0.CO;2-6

12. Mackie S, Morgan A, Jones P. Angiogenesis and giant cell arteritis. In: Slevin M editor. *Therapeutic angiogenesis for vascular diseases*. Dordrecht: Springer (2010). p. 383–402. doi: 10.1007/978-90-481-9495-7_17

13. Rodriguez-Pla A, Bosch-Gil J, Rossello-Urgell J, Huguet-Redecilla P, Stone J, Vilardell-Tarres M. Metalloproteinase–2 and –9 in giant cell arteritis: involvement in vascular remodeling. *Circulation.* (2005) 112:264–9. doi: 10.1161/CIRCULATIONAHA.104.520114

14. Brack A, Martinez-Taboada V, Stanson A, Goronzy J, Weyand C. Disease pattern in cranial and large-vessel giant cell arteritis. *Arthritis Rheum.* (1999) 42:311–7. doi: 10.1002/1529-0131(199902)42:23.0.CO;2-F

15. Kermani T, Warrington K, Crowson C, Ytterberg S, Hunder G, Gabriel S, et al. Large-vessel involvement in giant cell arteritis: a population-based cohort study of the incidence-trends and prognosis. *Ann Rheum Dis.* (2013) 72:1989–94. doi: 10.1136/annrheumdis-2012-202408

16. Prieto-González S, Arguis P, García-Martínez A, Espígol-Frigolé G, Tavera-Bahillo I, Butjosa M, et al. Large vessel involvement in biopsy-proven giant cell arteritis: prospective study in 40 newly diagnosed patients using CT angiography. *Ann Rheum Dis.* (2012) 71:1170–6. doi: 10.1136/annrheumdis-2011-200865

17. Andel P, Chrysidis S, Geiger J, Haaversen A, Haugeberg G, Myklebust G, et al. Diagnosing giant cell arteritis: a comprehensive practical guide for the practicing rheumatologist. *Rheumatology.* (2021) 60:4958–71. doi: 10.1093/rheumatology/keab547

18. Hemmig A, Gozzoli D, Werlen L, Ewald H, Aschwanden M, Blockmans D, et al. Subclinical giant cell arteritis in new onset polymyalgia rheumatica A systematic review and meta-analysis of individual patient data. *Semin Arthritis Rheum.* (2022) 55:152017. doi: 10.1016/j.semarthrit.2022.152017

19. Dejaco C, Duftner C, Buttgereit F, Matteson E, Dasgupta B. The spectrum of giant cell arteritis and polymyalgia rheumatica: revisiting the concept of the disease. *Rheumatology.* (2017) 56:506–15. doi: 10.1093/rheumatology/kew273

20. van der Geest K, Sandovici M, Brouwer E, Mackie S. Diagnostic accuracy of symptoms, physical signs, and laboratory tests for giant cell arteritis: a systematic review and meta-analysis. *Arch Intern Med.* (2020) 180:1295–304. doi: 10.1001/jamainternmed.2020.3050

21. Li K, Semenov D, Turk M, Pope J. A meta-analysis of the epidemiology of giant cell arteritis across time and space. *Arthritis Res Ther.* (2021) 23:82. doi: 10.1186/s13075-021-02450-w

22. Singh A, Kermani T, Crowson C, Weyand C, Matteson E, Warrington K. Visual manifestations in giant cell arteritis: trend over 5 decades in a population-based cohort. *J Rheumatol.* (2015) 42:309–15. doi: 10.3899/jrheum.140188

23. Vodopivec I, Rizzo J. Ophthalmic manifestations of giant cell arteritis. *Rheumatology.* (2018) 57(Suppl. 2):ii63–72. doi: 10.1093/rheumatology/kex428

24. Caselli R, Hunder G. Neurologic complications of giant cell (temporal) arteritis. *Semin Neurol.* (1994) 14:349–53. doi: 10.1055/s-2008-1041094

25. Razavi M, Jones R, Manzel K, Fattal D, Rizzo M. Steroid-responsive charles bonnet syndrome in temporal arteritis. *J Neuropsychiatry Clin Neurosci.* (2004) 16:505–8. doi: 10.1176/jnp.16.4.505

26. Monti S, Delvino P, Bellis E, Milanesi A, Brandolino F, Montecucco C. Impact of delayed diagnoses at the time of COVID-19: increased rate of preventable bilateral blindness in giant cell arteritis. *Ann Rheum Dis.* (2020) 79:1658–9. doi: 10.1136/annrheumdis-2020-217915

27. Cardoso C, Leite N, Dib E, Salles G. Predictors of development and progression of retinopathy in patients with type 2 diabetes: importance of blood pressure parameters. *Sci Rep.* (2017) 7:4867. doi: 10.1038/s41598-017-05159-6

28. Mursi A, Mirghani H, Elbeialy AA. A case report of post COVID19 giant cell arteritis and polymyalgia rheumatica with visual loss. *Clin Med Insights Case Rep.* (2022) 15:11795476221088472. doi: 10.1177/11795476221088472

29. Jonathan G, Scott F, Matthew KD. A case of post-COVID-19–Associated paracentral acute middle maculopathy and giant cell arteritis-like vasculitis. *J Neuro ophthalmol.* (2021) 41:351–5. doi: 10.1097/WNO.0000000000001348

30. Hayreh S, Zimmerman B. Management of giant cell arteritis. Our 27-year clinical study: new light on old controversies. *Ophthalmologica.* (2003) 217:239–59. doi: 10.1159/000070631

31. de Mornac D, Espitia O, Néel A, Connault J, Masseau A, Espitia-Thibault A, et al. Large-vessel involvement is predictive of multiple relapses in giant cell arteritis. *Ther Adv Musculoskelet Dis.* (2021) 13:1759720X211009029. doi: 10.1177/1759720X211009029

32. Deshayes S, Bourdin V, Creveuil C, Boutemy J, Liozon E, Kyndt X, et al. GLCCI1 polymorphism is associated with prednisone response in giant cell arteritis: a multicenter prospective study [abstract]. *Arthritis Rheumatol.* (2019) 71 (suppl 10). Available online at: https://acrabstracts.org/abstract/glcci1-polymorphism-is-associated-with-prednisone-response-in-giant-cell-arteritis-a-multicenter-prospective-study/ (accessed December 3, 2022).

33. Kermani T, Warrington K, Cuthbertson D, Carette S, Hoffman G, Khalidi N, et al. Disease relapses among patients with giant cell arteritis: a prospective, longitudinal cohort study. *J Rheumatol.* (2015) 42:1213–7. doi: 10.3899/jrheum.141347

34. Labarca C, Koster M, Crowson C, Makol A, Ytterberg S, Matteson E, et al. Predictors of relapse and treatment outcomes in biopsy-proven giant cell arteritis: a retrospective cohort study. *Rheumatology.* (2016) 55:347–56. doi: 10.1093/rheumatology/kev348

35. Hunder G, 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) 33:1122–8. doi: 10.1002/art.1780330810

36. Wiberg F, Naderi N, Mohammad A, Turesson C. Evaluation of revised classification criteria for giant cell arteritis and its clinical phenotypes. *Rheumatology.* (2021) 61:383–7. doi: 10.1093/rheumatology/keab353

37. Sait M, Lepore M, Kwasnicki R, Allington J, Balasubramanian R, Somasundaram S, et al. The 2016 revised ACR criteria for diagnosis of giant cell arteritis – our case series: can this avoid unnecessary temporal artery biopsies?. *Int J Surg Open.* (2017) 9:19–23. doi: 10.1016/j.ijso.2017.09.003

38. Ponte C, Grayson P, Robson J, Suppiah R, Gribbons K, Judge A, et al. 2022 american college of rheumatology/EULAR classification criteria for giant cell arteritis. *Ann Rheum Dis.* (2022) 81:1647–53. doi: 10.1136/ard-2022-223480

39. Narváez J, Bernad B, Roig-Vilaseca D, García-Gómez C, Gómez-Vaquero C, Juanola X, et al. Influence of previous corticosteroid therapy on temporal artery biopsy yield in giant cell arteritis. *Semin Arthritis Rheum.* (2007) 37:13–9. doi: 10.1016/j.semarthrit.2006.12.005

40. Rubenstein E, Maldini C, Gonzalez-Chiappe S, Chevret S, Mahr A. Sensitivity of temporal artery biopsy in the diagnosis of giant cell arteritis: a systematic literature review and meta-analysis. *Rheumatology.* (2020) 59:1011–20. doi: 10.1093/rheumatology/kez385

41. Maz M, Chung S, Abril A, Langford C, Gorelik M, Guyatt G, et al. 2021 american college of rheumatology/vasculitis foundation guideline for the management of giant cell arteritis and takayasu arteritis. *Arthritis Care Res.* (2021) 73:1071–87. doi: 10.1002/acr.24632

42. Hernández-Rodríguez J, Murgia G, Villar I, Campo E, Mackie S, Chakrabarty A, et al. Description and validation of histological patterns and proposal of a dynamic model of inflammatory infiltration in giant-cell arteritis. *Medicine.* (2016) 95:e2368. doi: 10.1097/MD.0000000000002368

43. Breuer G, Nesher R, Reinus K, Nesher G. Association between histological features in temporal artery biopsies and clinical features of patients with giant cell arteritis. *Isr Med Assoc J.* (2013) 15:271–4.

44. Schmidt W, Kraft H, Vorpahl K, Volker L, Gromnica-Ihle E. Color duplex ultrasonography in the diagnosis of temporal arteritis. *N Engl J Med.* (1997) 337:1336–42. doi: 10.1056/NEJM199711063371902

45. 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:e000612. doi: 10.1136/rmdopen-2017-000612

46. Chrysidis S, Døhn U, Terslev L, Fredberget U, Lorenzen T, Christensen R, et al. Diagnostic accuracy of vascular ultrasound in patients with suspected giant cell arteritis (EUREKA): a prospective, multicentre, non-interventional, cohort study. *Lancet Rheumatol.* (2021) 3:e865–73. doi: 10.1016/S2665-9913(21)00246-0

47. 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. *Health Technol Assess.* (2016) 20:1–238. doi: 10.3310/hta20900

48. Chrysidis S, Duftner C, Dejaco C, Schäfer V, Ramiro S, Carrara G, et al. Definitions and reliability assessment of elementary ultrasound lesions in giant cell arteritis: a study from the OMERACT large vessel vasculitis ultrasound working group. *RMD Open.* (2018) 4:e000598. doi: 10.1136/rmdopen-2017-000598

49. Evangelatos G, Grivas A, Pappa M, Kouna K, Iliopoulos A, Fragoulis G. Cranial giant cell arteritis mimickers: a masquerade to unveil. *Autoimmun Rev.* (2022) 21:103083. doi: 10.1016/j.autrev.2022.103083

50. Chrysidis S, Terslev L, Christensen R, Fredberg U, Larsen K, Lorenzen T, et al. Vascular ultrasound for the diagnosis of giant cell arteritis: a reliability and agreement study based on a standardised training programme. *RMD Open.* (2020) 6:e001337. doi: 10.1136/rmdopen-2020-001337

51. Aschwanden M, Imfeld S, Staub D, Baldi T, Walker U, Berger C, et al. The ultrasound compression sign to diagnose temporal giant cell arteritis shows an excellent interobserver agreement. *Clin Exp Rheumatol.* (2015) 33:S113–5.

52. van der Geest K, Borg F, Kayani A, Paap D, Gondo P, Schmidt W, et al. Novel ultrasonographic halo score for giant cell arteritis: assessment of diagnostic accuracy and association with ocular ischaemia. *Ann Rheum Dis.* (2020) 79:393–9. doi: 10.1136/annrheumdis-2019-216343

53. 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:S103–6.

54. Laskou F, Fiona C, Aung T, Benerjee S, Dasgupta B. 074 Fast track giant cell arteritis clinic and pathway for early management of suspected giant cell arteritis: an audit. *Rheumatology.* (2018) 57(Suppl. 3):key075. 298. doi: 10.1093/rheumatology/key075.298

55. Monti S, Bartoletti A, Bellis E, Delvino P, Montecucco C. Fast-track ultrasound clinic for the diagnosis of giant cell arteritis changes the prognosis of the disease but not the risk of future relapse. *Front Med.* (2020) 7:589794. doi: 10.3389/fmed.2020.589794

56. Sebastian A, Tomelleri A, Kayani A, Prieto-Pena D, Ranasinghe C, Dasgupta B. Probability-based algorithm using ultrasound and additional tests for suspected GCA in a fast-track clinic. *RMD Open.* (2020) 6:e001297. doi: 10.1136/rmdopen-2020-001297

57. Bosch P, Dejaco C, Schmidt W, Schlüter K, Pregartner G, Schäfer V. Association of ultrasound-confirmed axillary artery vasculitis and clinical outcomes in giant cell arteritis. *Semin Arthritis Rheum.* (2022) 56:152051. doi: 10.1016/j.semarthrit.2022.152051

58. Prearo I, Dekorsy F, Brendel M, Lottspeich C, Dechant C, Schulze-Koops H, et al. Diagnostic yield of axillary artery ultrasound in addition to temporal artery ultrasound for the diagnosis of giant cell arteritis. *Clin Exp Rheumatol.* (2022) 40:819–25. doi: 10.55563/clinexprheumatol/v1bvfz

59. Bull Haaversen A, Brekke L, Kermani T, Molberg Ø, Diamantopoulos A. Extended ultrasound examination identifies more large vessel involvement in patients with giant cell arteritis. *Rheumatology.* (2022). [Epub ahead of print]. doi: 10.1093/rheumatology/keac478

60. Skoog J, Svensson C, Eriksson P, Sjöwall C, Zachrisson H. The diagnostic performance of an extended ultrasound protocol in patients with clinically suspected giant cell arteritis. *Front Med.* (2021) 8:807996. doi: 10.3389/fmed.2021.807996

61. Kung B, Seraj S, Zadeh M, Rojulpote C, Kothekar E, Ayubcha C, et al. An update on the role of 18F-FDG-PET/CT in major infectious and inflammatory diseases. *Am J Nucl Med Mol Imaging.* (2019) 9:255–73.

62. Nienhuis P, Sandovici M, Glaudemans A, Slart R, Brouwer E. Visual and semiquantitative assessment of cranial artery inflammation with FDG-PET/CT in giant cell arteritis. *Semin Arthritis Rheum.* (2020) 50:616–23. doi: 10.1016/j.semarthrit.2020.04.002

63. Sammel A, Hsiao E, Schembri G, Nguyen K, Brewer J, Schrieber L, et al. Diagnostic accuracy of positron emission tomography/computed tomography of the head, neck, and chest for giant cell arteritis: a prospective, Double-Blind, Cross-Sectional study. *Arthritis Rheumatol.* (2019) 71:1319–28. doi: 10.1002/art.40864

64. Thibault T, Durand-Bailloud B, Soudry-Faure A, Greigert H, Drouet C, Devilliers H, et al. PET/CT of cranial arteries for a sensitive diagnosis of giant cell arteritis. *Rheumatology.* (2022). [Epub ahead of print]. doi: 10.1093/rheumatology/keac430

65. Klink T, Geiger J, Both M, Ness T, Heinzelmann S, Reinhard M, et al. Giant cell arteritis: diagnostic accuracy of MR imaging of superficial cranial arteries in initial Diagnosis–Results from a multicenter trial. *Radiology.* (2014) 273:844–52. doi: 10.1148/radiol.14140056

66. Cerne J, Liu S, Umair M, Pathrose A, Moore JE, Allen BD, et al. Combined modality PET/MR for the detection of severe large vessel vasculitis. *Eur J Hybrid Imaging.* (2022) 6:16. doi: 10.1186/s41824-022-00136-3

67. Padoan R, Crimì F, Felicetti M, Padovano F, Lacognata C, Stramare R, et al. Fully integrated [18F]FDG PET/MR in large vessel vasculitis. *Q J Nucl Med Mol Imaging.* (2022) 66:272–9. doi: 10.23736/S1824-4785.19.03184-4

68. van der Geest K, Treglia G, Glaudemans A, Brouwer E, Sandovici M, Jamar F, et al. Diagnostic value of [18F]FDG-PET/CT for treatment monitoring in large vessel vasculitis: a systematic review and meta-analysis. *Eur J Nucl Med Mol Imaging.* (2021) 48:3886–902. doi: 10.1007/s00259-021-05362-8

69. Nielsen B, Gormsen L, Hansen I, Keller K, Therkildsen P, Hauge E. Three days of high-dose glucocorticoid treatment attenuates large-vessel 18F-FDG uptake in large-vessel giant cell arteritis but with a limited impact on diagnostic accuracy. *Eur J Nucl Med Mol Imaging.* (2018) 45:1119–28. doi: 10.1007/s00259-018-4021-4

70. Blockmans D, 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. *Rheumatology.* (2008) 47:1179–84. doi: 10.1093/rheumatology/ken119

71. Malich L, Gühne F, Hoffmann T, Malich A, Weise T, Oelzner P, et al. Distribution patterns of arterial affection and the influence of glucocorticoids on 18F-fluorodeoxyglucose positron emission tomography/CT in patients with giant cell arteritis. *RMD Open.* (2022) 8:e002464. doi: 10.1136/rmdopen-2022-002464

72. van der Veen E, Suurs F, Cleeren F, Bormans G, Elsinga P, Hospers G, et al. Development and evaluation of interleukin-2 derived radiotracers for PET imaging of T-cells in mice. *J Nucl Med.* (2020) 61:1355–60. doi: 10.2967/jnumed.119.238782

73. Lamare F, Hinz R, Gaemperli O, Pugliese F, Mason J, Spinks T, et al. Detection and quantification of large-vessel inflammation with 11C-(R)-PK11195 PET/CT. *J Nucl Med.* (2011) 52:33–9. doi: 10.2967/jnumed.110.079038

74. Pugliese F, Gaemperli O, Kinderlerer A, Lamare F, Shalhoub J, Davies A, et al. Imaging of vascular inflammation with [11 C]-PK11195 and positron emission tomography/computed tomography angiography. *J Am Coll Cardiol.* (2010) 56:653–61. doi: 10.1016/j.jacc.2010.02.063

75. van der Geest K, Sandovici M, Nienhuis P, Slart R, Heeringa P, Brouwer E. Novel PET imaging of inflammatory targets and cells for the diagnosis and monitoring of giant cell arteritis and polymyalgia rheumatica. *Front Med.* (2022) 9:902155. doi: 10.3389/fmed.2022.902155

76. Lecler A, Hage R, Charbonneau F, Vignal C, Sené T, Picard H, et al. Validation of a multimodal algorithm for diagnosing giant cell arteritis with imaging. *Diagn Interv Imaging.* (2022) 103:103–10. doi: 10.1016/j.diii.2021.09.008

77. Bley T, Reinhard M, Hauenstein C, Markl M, Warnatz K, Hetzel A, et al. Comparison of duplex sonography and high-resolution magnetic resonance imaging in the diagnosis of giant cell (temporal) arteritis. *Arthritis Rheum.* (2008) 58:2574–8. doi: 10.1002/art.23699

78. Yip A, Jernberg E, Bardi M, Geiger J, Lohne F, Schmidt W, et al. Magnetic resonance imaging compared to ultrasonography in giant cell arteritis: a cross-sectional study. *Arthritis Res Ther.* (2020) 22:247. doi: 10.1186/s13075-020-02335-4

79. Conway R, Smyth A, Kavanagh R, O'Donohoe R, Purcell Y, Heffernan E. Diagnostic utility of computed tomographic angiography in giant-cell arteritis. *Stroke.* (2018) 49:2233–6. doi: 10.1161/STROKEAHA.118.021995

80. Moragas Solanes M, Andreu Magarolas M, Martín Miramon J, Caresia Aróztegui A, Monteagudo Jiménez M, Oliva Morera J, et al. Comparative study of 18F-FDG PET/CT and CT angiography in detection of large vessel vasculitis. *Rev Esp Med Nucl Imagen Mol.* (2019) 38:280–9. doi: 10.1016/j.remn.2019.03.002

81. Vaidyanathan S, Chattopadhyay A, Mackie S, Scarsbrook A. Comparative effectiveness of 18F-FDG PET-CT and contrast-enhanced CT in the diagnosis of suspected large-vessel vasculitis. *Br J Radiol.* (2018) 91:20180247. doi: 10.1259/bjr.20180247

82. 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) 77:636–43. doi: 10.1136/annrheumdis-2017-212649

83. Mackie S, Dejaco C, Appenzeller S, Camellino D, Duftner C, Gonzalez-Chiappe S, et al. British society for rheumatology guideline on diagnosis and treatment of giant cell arteritis. *Rheumatology.* (2020) 59:E1–23. doi: 10.1093/rheumatology/kez672

84. Kanakamedala A, Hussain M, Kini A, Al Othman B, Lee A. Corticosteroid usage in giant cell arteritis. *Neuroophthalmology.* (2021) 45:17–22. doi: 10.1080/01658107.2020.1767656

85. Wilson J, Sarsour K, Collinson N, Tuckwell K, Musselman D, Klearman M, et al. Serious adverse effects associated with glucocorticoid therapy in patients with giant cell arteritis (GCA): a nested case-control analysis. *Semin Arthritis Rheum.* (2016) 46:819–27. doi: 10.1016/j.semarthrit.2016.11.006

86. Gale S, Wilson J, Chia J, Trinh H, Tuckwell K, Collinson N, et al. Risk associated with cumulative oral glucocorticoid use in patients with giant cell arteritis in real-world databases from the USA and UK. *Rheumatol Ther.* (2018) 5:327–40. doi: 10.1007/s40744-018-0112-8

87. Mahr A, Hachulla E, de Boysson H, Guerroui N, Héron E, Vinzio S, et al. Presentation and real-world management of giant cell arteritis (artemis study). *Front Med.* (2021) 8:732934. doi: 10.3389/fmed.2021.732934

88. 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) 19:495–501.

89. Hoffman G, Cid M, Hellmann D, Guillevin L, Stone J, Schousboe J, et al. A multicenter, randomized, double-blind, placebo-controlled trial of adjuvant methotrexate treatment for giant cell arteritis. *Arthritis Rheum.* (2002) 46:1309–18. doi: 10.1002/art.10262

90. Jover J, Hernandez-Garcia C, Morado I, Vargas E, Banares A, Fernandez-Gutierrez B. Combined treatment of giant-cell arteritis with methotrexate and prednisone : a randomized, double-blind, placebo-controlled trial. *Ann Intern Med.* (2001) 134:106–14. doi: 10.7326/0003-4819-134-2-200101160-00010

91. Mahr A, Jover J, Spiera R, Hernández-García C, Fernández-Gutiérrez B, Lavalley M, et al. Adjunctive methotrexate for treatment of giant cell arteritis: an individual patient data meta-analysis. *Arthritis Rheum.* (2007) 56:2789–97. doi: 10.1002/art.22754

92. Gérard A, Simon-Tillaux N, Yordanov Y, Cacoub P, Tubach F, Saadoun D, et al. Efficacy and safety of steroid-sparing treatments in giant cell arteritis according to the glucocorticoids tapering regimen: a systematic review and meta-analysis. *Eur J Intern Med.* (2021) 88:96–103. doi: 10.1016/j.ejim.2021.03.040

93. De Silva M, Hazleman B. Azathioprine in giant cell arteritis/polymyalgia rheumatica: a double-blind study. *Ann Rheum Dis.* (1986) 45:136–8. doi: 10.1136/ard.45.2.136

94. 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) 35:327–9. doi: 10.1080/03009740500474537

95. Ly K, Dalmay F, Gondran G, Palat S, Bezanahary H, Cypierre A, et al. Steroid-sparing effect and toxicity of dapsone treatment in giant cell arteritis: a single-center, retrospective study of 70 patients. *Medicine.* (2016) 95:e4974. doi: 10.1097/MD.0000000000004974

96. de Souza A, da Silva M, Machado L, Oliveira A, Pinheiro F, Sato E. Short-term effect of leflunomide in patients with takayasu arteritis: an observational study. *Scand J Rheumatol.* (2012) 41:227–30. doi: 10.3109/03009742.2011.633553

97. Breedveld F, Dayer J. Leflunomide: mode of action in the treatment of rheumatoid arthritis. *Ann Rheum Dis.* (2000) 59:841–9. doi: 10.1136/ard.59.11.841

98. 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 Pract.* (2012) 66:906–9. doi: 10.1111/j.1742-1241.2012.02981.x

99. Diamantopoulos A, Hetland H, Myklebust G. Leflunomide as a corticosteroid-sparing agent in giant cell arteritis and polymyalgia rheumatica: a case series. *Biomed Res Int.* (2013) 2013:120638. doi: 10.1155/2013/120638

100. Hocevar A, Jese R, Rotar Z, Tomsic M. Does leflunomide have a role in giant cell arteritis? an open-label study. *Clin Rheumatol.* (2019) 38:291–6. doi: 10.1007/s10067-018-4232-x

101. Tengesdal S, Diamantopoulos A, Myklebust G. Leflunomide versus methotrexate in treatment of giant cell arteritis: comparison of efficacy, safety, and drug survival. *Scand J Rheumatol.* (2019) 48:333–5. doi: 10.1080/03009742.2019.1575980

102. Deshayes S, Ly K, Rieu V, Maigné G, Martin Silva N, Manrique A, et al. Steroid-sparing effect of anakinra in giant-cell arteritis: a case series with clinical, biological and iconographic long-term assessments. *Rheumatology.* (2021) 61:400–6. doi: 10.1093/rheumatology/keab280

103. Higuchi T, Nakanishi T, Takada K, Matsumoto M, Okada M, Horikoshi H, et al. A case of multicentric castleman's disease having lung lesion successfully treated with humanized anti-interleukin-6 receptor antibody, tocilizumab. *J Korean Med Sci.* (2010) 25:1364–7. doi: 10.3346/jkms.2010.25.9.1364

104. Stone J, Tuckwell K, Dimonaco S, Klearman M, Aringer M, Blockmans D, et al. Trial of tocilizumab in giant-cell arteritis. *N Engl J Med.* (2017) 377:317–28. doi: 10.1056/NEJMoa1613849

105. Calderón-Goercke M, Loricera J, Aldasoro V, Castañeda S, Villa I, Humbría A, et al. Tocilizumab in giant cell arteritis. observational, open-label multicenter study of 134 patients in clinical practice. *Semin Arthritis Rheum.* (2019) 49:126–35. doi: 10.1016/j.semarthrit.2019.01.003

106. Regola F, Cerudelli E, Bosio G, Andreoli L, Tincani A, Franceschini F, et al. Long-term treatment with tocilizumab in giant cell arteritis: efficacy and safety in a monocentric cohort of patients. *Rheumatol Adv Pract.* (2020) 4:rkaa017. doi: 10.1093/rap/rkaa017

107. Hellmich B, Agueda A, Monti S, Buttgereit F, de Boysson H, Brouwer E, et al. 2018 update of the EULAR recommendations for the management of large vessel vasculitis. *Ann Rheum Dis.* (2020) 79:19–30. doi: 10.1136/annrheumdis-2019-215672

108. Schmitt C, Brockwell L, Giraudon M, Zucchetto M, Christ L, Bannert B, et al. Intravenous tocilizumab for the treatment of giant cell arteritis: a phase Ib dose-ranging pharmacokinetic bridging study. *Arthritis Res Ther.* (2022) 24:133. doi: 10.1186/s13075-022-02815-9

109. Conway R, O'Neill L, O'Flynn E, Gallagher P, McCarthy G, Murphy C, et al. Ustekinumab for the treatment of refractory giant cell arteritis. *Ann Rheum Dis.* (2016) 75:1578–9. doi: 10.1136/annrheumdis-2016-209351

110. Matza M, Fernandes A, Stone J, Unizony S. Ustekinumab for the treatment of giant cell arteritis. *Arthritis Care Res.* (2021) 73:893–7. doi: 10.1002/acr.24200

111. Langford C, Cuthbertson D, Ytterberg S, Khalidi N, Monach P, Carette S, et al. A randomized, Double-Blind trial of abatacept (CTLA-4Ig) for the treatment of giant cell arteritis. *Arthritis Rheumatol.* (2017) 69:837–45. doi: 10.1002/art.40044

112. Rossi D, Cecchi I, Sciascia S, Naretto C, Alpa M, Roccatello D. An agent-to-agent real life comparison study of tocilizumab versus abatacept in giant cell arteritis. *Clin Exp Rheumatol.* (2021) 39:125–8. doi: 10.55563/clinexprheumatol/l0hd9v

113. Cantini F, Niccoli L, Salvarani C, Padula A, Olivieri I. Treatment of longstanding active giant cell arteritis with infliximab: report of four cases. *Arthritis Rheum.* (2001) 44:2933–5. doi: 10.1002/1529-0131(200112)44:123.0.CO;2-Y

114. Airoldi P, Antonioli C, Vianelli M, Toniati P. Anti-tumour necrosis factor treatment with infliximab in a case of giant cell arteritis resistant to steroid and immunosuppressive drugs. *Br J Rheumatol.* (2002) 41:347–9. doi: 10.1093/rheumatology/41.3.347

115. Uthman I, Kanj N, Atweh S. Infliximab as monotherapy in giant cell arteritis. *Clin Rheumatol.* (2006) 25:109–10. doi: 10.1007/s10067-005-1115-8

116. Torrente S, Güerri R, Pérez-García C, Benito P, Carbonell J. Amaurosis in patients with giant cell arteritis: treatment with anti-tumour necrosis factor-α. *Intern Med J.* (2007) 37:280–1. doi: 10.1111/j.1445-5994.2006.01299.x

117. Hoffman G, Cid M, 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) 146:621–30. doi: 10.7326/0003-4819-146-9-200705010-00004

118. Martínez-Taboada V, 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) 67:625–30. doi: 10.1136/ard.2007.082115

119. 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) 73:2074–81. doi: 10.1136/annrheumdis-2013-203586

120. Bursi R, Cafaro G, Perricone C, Riccucci I, Calvacchi S, Gerli R, et al. Contribution of janus-kinase/signal transduction activator of transcription pathway in the pathogenesis of vasculitis: a possible treatment target in the upcoming future. *Front Pharmacol.* (2021) 12:635663. doi: 10.3389/fphar.2021.635663

121. Zhang H, Watanabe R, Berry G, Tian L, Goronzy J, Weyand C. Inhibition of JAK-STAT signaling suppresses pathogenic immune responses in medium and large vessel vasculitis. *Circulation.* (2018) 137:1934–48. doi: 10.1161/CIRCULATIONAHA.117.030423

122. Koster M, Crowson C, Giblon R, Jaquith J, Duarte-García A, Matteson E, et al. Baricitinib for relapsing giant cell arteritis: a prospective open-label 52-week pilot study. *Ann Rheum Dis.* (2022) 81:861–7. doi: 10.1136/annrheumdis-2021-221961

123. Burmester G, Feist E, Sleeman M, Wang B, White B, Magrini F. Mavrilimumab, a human monoclonal antibody targeting GM-CSF receptor-α, in subjects with rheumatoid arthritis: a randomised, double-blind, placebo-controlled, phase I, first-in-human study. *Ann Rheum Dis.* (2011) 70:1542–9. doi: 10.1136/ard.2010.146225

124. Cid M, Unizony S, Blockmans D, Brouwer E, Dagna L, Dasgupta B, et al. Efficacy and safety of mavrilimumab in giant cell arteritis: a phase 2, randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis.* (2022) 81:653–61. doi: 10.1136/annrheumdis-2021-221865

125. de Franciscis S, Roscitano G, Serra R, Buffone G, Cotroneo A, de Franciscis A, et al. Combined medical, surgical and endovascular treatment of a giant cell arteritis case manifesting as upper limbs acute ischemia. *Int J Surg Case Rep.* (2011) 2:71–3. doi: 10.1016/j.ijscr.2011.02.003

126. Dementovych N, Mishra R, Shah Q. Angioplasty and stent placement for complete occlusion of the vertebral artery secondary to giant cell arteritis. *J Neurointerv Surg.* (2012) 4:110–3. doi: 10.1136/jnis.2011.004689

127. Simonsen C, Speiser L, Hansen I, Jayne D, von Weitzel-Mudersbach P. Endovascular treatment of intracerebral giant cell arteritis. *Front Neurol.* (2020) 11:287. doi: 10.3389/fneur.2020.00287

128. Caton M Jr., Mark I, Narsinh K, Baker A, Cooke D, Hetts S, et al. Endovascular therapy for intracranial giant cell arteritis : systematic review, technical considerations and the effect of intra-arterial calcium channel blockers. *Clin Neuroradiol.* (2022). [Epub ahead of print]. doi: 10.1007/s00062-022-01171-0

129. Christ L, Seitz L, Scholz G, Sarbu A, Amsler J, Bütikofer L, et al. Tocilizumab monotherapy after ultra-short glucocorticoid administration in giant cell arteritis: a single-arm, open-label, proof-of-concept study. *Lancet Rheumatol.* (2021) 3:e619–26. doi: 10.1016/S2665-9913(21)00152-1

130. Unizony S, Matza M, Jarvie A, Fernandes A, Stone JH. OP0185 tocilizumab in combination with 8 weeks of prednisone for giant cell arteritis. *Ann Rheum Dis.* (2022) 81:123.

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EDITED BY
Andreas P. Diamantopoulos,
Akershus University Hospital, Norway

REVIEWED BY
Alojzija Hocevar,
University Medical Center
Ljubljana, Slovenia
Gerasimos Evangelatos,
National and Kapodistrian University of
Athens, Greece

*CORRESPONDENCE
Marcin Milchert
marcmilc@hotmail.com

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Intima-media thickness cut-off values depicting "halo sign" and potential confounder analysis for the best diagnosis of large vessel giant cell arteritis by ultrasonography

Marcin Milchert*, Jacek Fliciński and Marek Brzosko

Department of Internal Medicine, Rheumatology, Diabetology, Geriatrics and Clinical Immunology, Pomeranian Medical University, Szczecin, Poland

Background: Vascular ultrasound enables fast-track diagnosis of giant cell arteritis (GCA), but this method remains subjective. We aimed to determine intima-media thickness (IMT) cut-off values for large vessel GCA (LV-GCA) and identify the clinically relevant factors influencing it.

Methods: We included 214 patients referred for ultrasound evaluation within a fast-track clinic due to suspected GCA. IMT was measured in axillary, brachial, subclavian, superficial femoral, and common carotid arteries (CCA), in a place without identifiable atherosclerotic plaques. IMT cut-off values for vasculitis were determined by comparing measurements in arteries classified as vasculitis vs. controls without GCA/polymyalgia rheumatica (PMR).

Results: Giant cell arteritis was diagnosed in 81 individuals, including extracranial LV-GCA in 43 individuals. Isolated PMR was diagnosed in 50 subjects. In 83 remaining patients, another diagnosis was confirmed, and they served as controls. The rounded optimal IMT cut-off values for the diagnosis of axillary vasculitis were 0.8 mm, subclavian-0.7 mm, superficial femoral-0.9 mm, CCA-0.7 mm, and brachial-0.5 mm. The IMT cut-off values providing 100% specificity for vasculitis (although with reduced sensitivity) were obtained with axillary IMT 1.06 mm, subclavian-1.35 mm, superficial femoral-1.55 mm, CCA-1.27 mm, and brachial-0.96 mm. Axillary and subclavian arteritis provided the best AUC for the diagnosis of GCA, while carotid and axillary were most commonly involved (24 and 23 patients, respectively). The presence of calcified atherosclerotic plaques was related to an increase of IMT in both patients and controls, while male sex, age $\geq$ 68, hypertension, and smoking increased IMT in controls but not in patients with GCA.

Conclusion: Cut-off values for LV-GCA performed best in axillary and subclavian arteritis but expanding examination to the other arteries may add to the sensitivity of GCA diagnosis (another location, e.g., brachial arteritis) and its specificity (identification of calcified atherosclerotic plaques in other arteries such as CCA, which may suggest applying higher IMT cut-off values).

We proposed a more linear approach to cut-off values with two values: one for the most accurate and the other for a highly specific diagnosis and also considering some cardiovascular risk factors.

KEYWORDS

giant cell arteritis, arteriosclerosis, vasculitis, ultrasound, halo sign, reference range

Key messages

- Intima-media cut-off values for large vessel GCA perform best in axillary and subclavian arteritis.
- Expanding examination to multiple arteries adds to the diagnostic sensitivity and specificity.
- The presence of some cardiovascular risk factors (male sex, age $\geq$ 68, hypertension, smoking, and the presence of calcified atherosclerotic plaques) may confound intima-media cut-off values.
- We proposed prior confounder analysis to apply cut-off values with two values: one for most accurate and the other for highly specific diagnosis.

Introduction

Diagnosis of giant cell arteritis (GCA) with large vessel involvement is delayed compared to temporal arteritis but is improving, thanks to the wider implementation of imaging in clinical practice (1, 2). Ultrasound-based fast-track clinics enable fast diagnosis of GCA and rapid initiation of treatment to prevent disease complications (3). Ultrasonography is a promising method for the diagnosis of not only temporal arteritis (4) but also extracranial, large vessel GCA (LV-GCA) (5–9). Compared to temporal artery biopsy, color duplex ultrasonography (CDU) offers faster results and is non-invasive and cost-effective, while serving high sensitivity and specificity (10). The most important ultrasonographic sign of large artery wall inflammation is an increase of intima-media thickness (IMT) with some characteristic features known as the "halo sign" (Figure 1) (11, 12). However, in elderly patients with GCA, atherosclerosis is common and requires careful differentiation with an increase of IMT caused by vasculitis (13, 14). Observer dependency and lack of standardization of the ultrasound method remain major concerns. Modern high-frequency ultrasound probes provide resolutions that enable exact vessel wall thickness measurements. There is a need to define IMT consistent with the halo sign for the diagnosis of GCA and identify the potential factors that influence IMT. Therefore, we aimed to determine IMT cut-off values for LV-GCA in a real-life scenario considering patients' cardiovascular risk factors as potential confounders.

Materials and methods

Study population

Between April 2011 and June 2015, 312 patients suspected of GCA were referred for CDU evaluation within a fast-track GCA clinic. Referrals for GCA evaluation were not limited, and they included ophthalmological manifestations, other manifestations of cranial GCA, polymyalgia rheumatica (PMR) manifestations, pyrexia of unknown origin, and others. All consecutive, confirmed GCA cases were included but 98 controls (negative temporal and large vessel CDU and low clinical probability of GCA) were not included due to the loss of follow-up. They were not referred back for GCA reevaluation although our department is the only local reference center for vasculitis. We included isolated PMR as a distinct subgroup in the analysis to evaluate possible atherosclerosis in this subgroup and its risk factors. We finally included 214 subjects in the study. A history of hypertension, smoking, and diabetes mellitus was assessed. Arterial hypertension was defined as systolic blood pressure of $\geq$140 mm Hg and/or diastolic blood pressure of $\geq$90 mm Hg. Diabetes mellitus was defined in accordance with the Polish Society of Diabetology guidelines as a positive oral glucose tolerance test, a random glucose level of $\geq$200 mg/dl with clinical manifestations, or with fasting glucose of $\geq$126 mg/dl. Hypercholesterolemia was defined as an LDL cholesterol level of $\geq$115 mg/dl. Smoking was noted in case of a history of $>$3 pack years of smoking. Fasting lipid profiles were measured or retrieved from the medical records (within 1 year prior to GCA diagnosis) in 137 patients. Temporal artery biopsy (TAB) was performed in 44 patients, and contrasted computed tomography (CT) of the thoracic and abdominal aorta was performed in 126 patients. The research was approved by the decision KB-0012/111/10 and KB-0012/12/14 of the Local Ethical Committee.

GCA diagnosis

Final GCA and PMR diagnoses were established by a team of a minimum of two experienced rheumatologists and confirmed in at least one follow-up visit within 9 months. Patients with cranial GCA met ACR criteria (15). Large vessel GCA diagnosis

was confirmed by arterial ultrasound and/or aortic CT (defined as circumferential, long-segmental aortic wall thickening of ≥3 or ≥2 mm with adjacent adventitia involvement) together with the presence of GCA or PMR manifestations. Patients with PMR met the 2012 EULAR/ACR classification criteria (16).

Ultrasound examination

All CDU, together with categorization into arteritis and non-arteritis findings, were performed before or within 3 days after treatment initiation, by a single physician (M.M.), experienced with performing >800 ultrasound examinations in suspected LV-GCA. He was blinded to diagnosis but aware of clinical presentation. Bilateral CDU examination of brachial, axillary, subclavian, superficial femoral, and common carotid arteries (CCA) was performed in all patients in both transverse and longitudinal planes. Halo sign definition was consistent with the one formulated by OMERACT: homogenous, hypoechoic wall thickening, well-delineated toward the luminal side, visible both in longitudinal and transverse planes, and most commonly concentric in transverse scans (11). Maximal IMT was measured from vessel lumen to media-adventitia interface, in mm with two decimals, in a place without identifiable atherosclerotic plaques, preferably on the distal wall. Maximal IMT from the left and right side locations were noted as well as mean IMT of corresponding left and right side measurements were calculated, which has to be included in further analysis. IMT cut-off values for vasculitis were determined by comparing measurements in arteries classified as vasculitis vs. controls. Additionally, measurements in arteries classified as vasculitis were compared with corresponding locations in GCA without large vessel vasculitis. The presence of calcified atherosclerotic plaques covering over 25% of vessel lumen in carotid bulbs and femoral arteries was assessed with CDU and noted. Esaote MyLab25Gold machine with 5–10 and 10–18 MHz linear probes was used.

Statistical analysis

Receiver operating characteristic (ROC) curves were calculated (Figure 2). Minimal difference between sensitivity and 1- specificity was chosen for optimal IMT cut-off values for

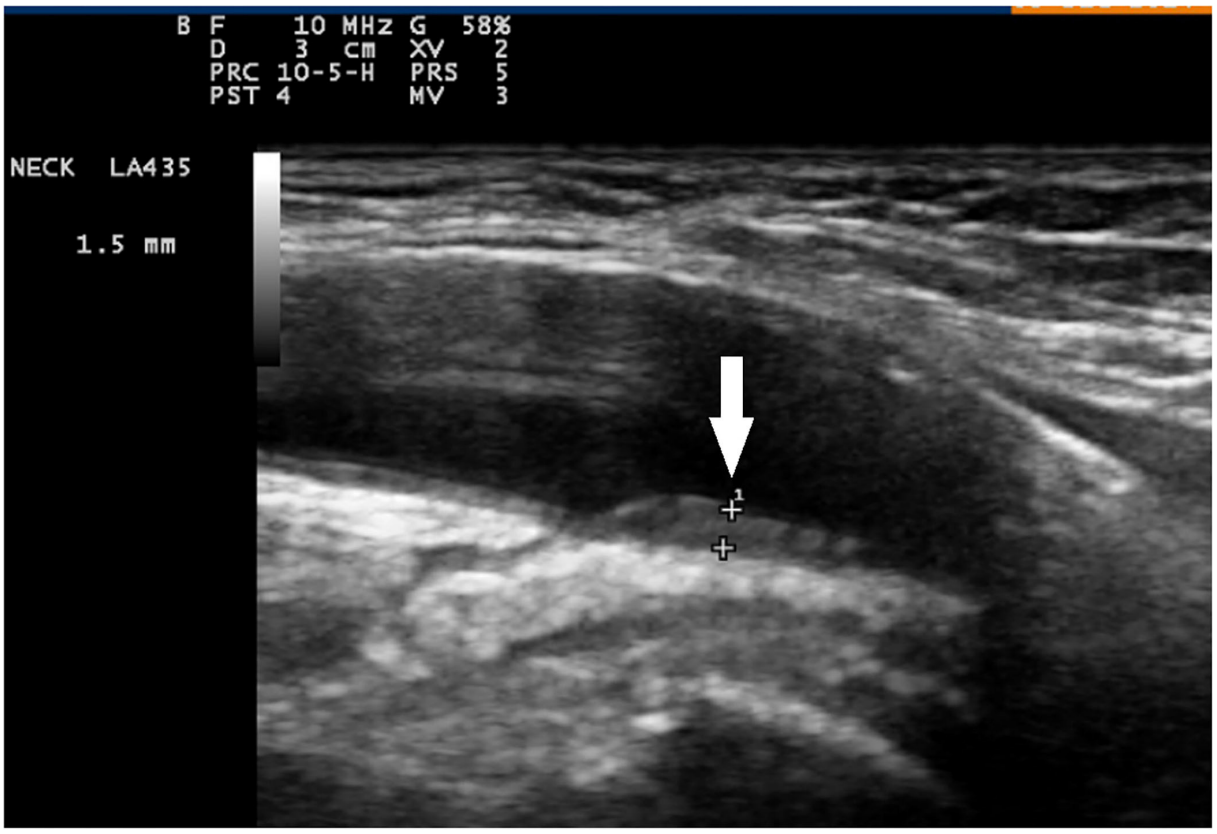

FIGURE 1
Color duplex sonography of axillary artery and longitudinal plane. Signs of vasculitis in an axillary artery (arrow) sliding down to a normal intima-media in the brachial artery (slope sign).

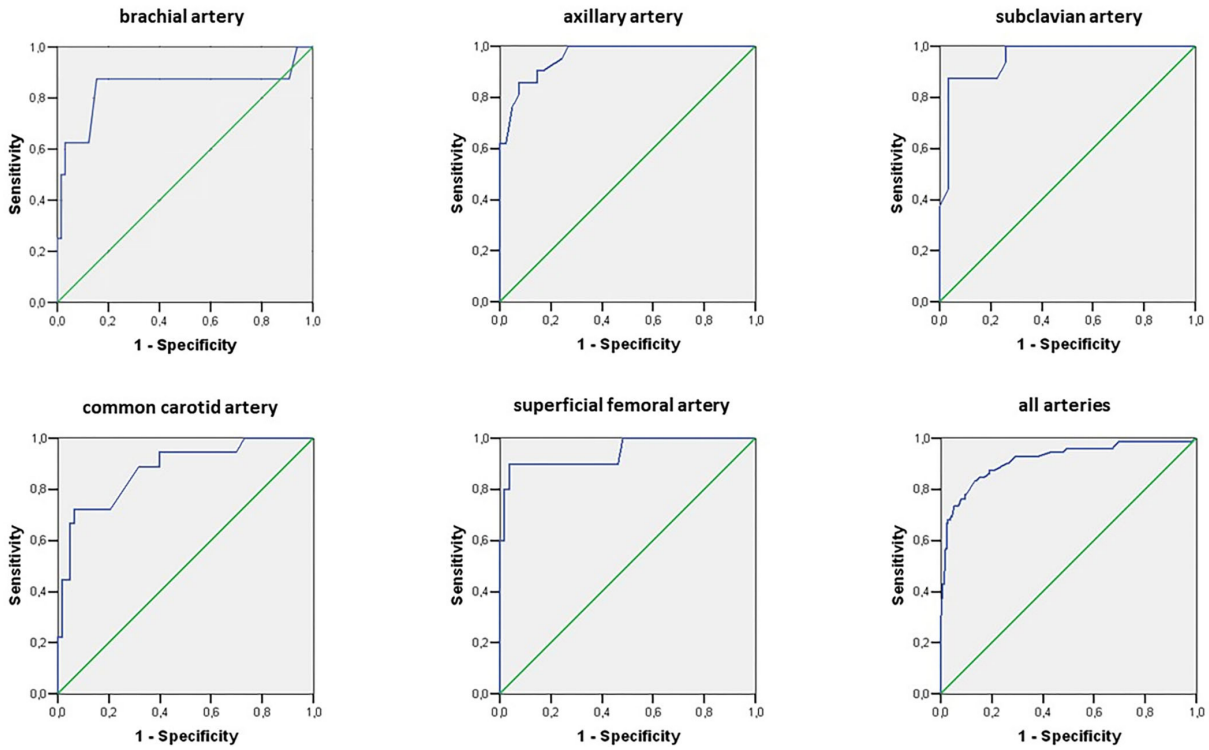

FIGURE 2
Receiver operating characteristic (ROC) curves for cut-off values of intima-media thickness (IMT) depicting vasculitis in patients with giant cell arteritis. The maximal IMT value from bilateral color duplex ultrasonography measurements was chosen.

vasculitis. Mann-Whitney and χ^2 Pearson tests were used to compare between groups. Intrarater reliability was calculated from repeated measurements in 21 vessels of 5 patients and controls. For interrater reliability, 51 IMT measurements in 10 patients and controls were additionally performed by JF. Both readers underwent similar training and used the same equipment. Concordance correlation coefficients for intrarater and interrater reliability were calculated. The $p < 0.05$ were considered to be significant. Statistical analysis was performed using STATA software (version 12.0; StataCorp).

Results

Study population

Giant cell arteritis was diagnosed in 81 individuals (TAB was positive for GCA in 31/44 biopsied patients), PMR in 131, and isolated PMR (without concomitant GCA) in 50 patients. Aortitis was diagnosed in 39 out of 126 patients based on CT. Extracranial LV-GCA was diagnosed in 43 patients. In the remaining 83 patients, another diagnosis was confirmed, and they served as non-GCA/PMR controls. Study population characteristics are included in Table 1. Notably, 5 patients with GCA failed to follow up. In the remaining, the diagnosis was sustained. None of the patients with non-GCA were reclassified to GCA. Patients with GCA were significantly older by a mean of 8 years compared with the controls (73 ± 9 vs. 65 ± 10 years). Calcified atherosclerotic plaques covering over 25% of the vessel lumen were significantly less common in isolated PMR compared to GCA and controls. Other patients' characteristics potentially confounding IMT were similar (Table 2). The number of patients referred by different medical specialists is presented in Supplementary Table 1.

IMT measurements

In controls but not in patients with GCA, mean IMT was influenced by age, gender, hypertension, and smoking. The presence of calcified atherosclerotic plaques was associated with increased IMT in PMR, GCA, and controls (Table 3). In LV-GCA cases, IMT in brachial, axillary, subclavian, femoral, and carotid arteries was significantly higher in both vs. controls and isolated PMR. In isolated cranial GCA, large vessel IMT did not differ vs. controls (Table 4). Left CCA IMT was higher compared to the right side in GCA (0.76 ± 0.28 vs. 0.67 ± 0.26; $p = 0.011$) with no significant left to right differences in other arteries in

TABLE 1 Subtypes of GCA and PMR and structure of controls characterizing 214 included patients.

Subtypes of GCA and PMR	*N* (%)	Structure of non-GCA/PMR controls (*N* = 83)	*N* (%)
GCA	81	Rheumatoid arthritis	26 (31)
Extracranial LV-GCA*	43 (53)	Osteoarthritis	12 (14)
Aortitis	39 (48)**	Infections	7 (8)
Axillary arteritis	23 (28)	Neoplasms	6 (7)
Subclavian arteritis	18 (22)	Atherosclerosis with related complications	5 (6)
Superficial femoral arteritis	11 (14)	Migraine	4 (5)
Brachial arteritis	8 (10)***	Fibromyalgia	3 (4)
PMR	131	Vasculitis (other than GCA)	3 (4)
Isolated PMR****	50	Systemic lupus erythematosus	3 (4)
		Spondyloarthropathies	2 (2)
		Neuralgias	2 (2)
		Others	10 (12)

*At least unilateral vasculitis in the large vessel was required to classify the case as GCA, **based on CT performed in 126 patients, ***all but one spreading per continuum from axillary arteritis, and ****without concomitant GCA. GCA, giant cell arteritis; PMR, polymyalgia rheumatica.

TABLE 2 The characteristics of patients.

	GCA (*N* = 81)	Isolated PMR (*N* = 50)	Non-GCA/PMR controls (*N* = 83)
Female/male	53 (65%)/28 (35%)	37 (74%)/13 (26%)	54 (65%)/29 (35%)
Age (years, mean ± SD; min-max)	73* ± 9; 55–95	69 ± 9; 52–87	65 ± 10; 44–89
Hypertension	53 (65%)	31 (62%)	44 (53%)
Smoking	36 (44%)	14 (28%)	29 (35%)
Diabetes mellitus	13 (16%)	6 (12%)	15 (18%)
Hypercholesterolemia	25/66 (38%)	12/33 (36%)	19/38 (50%)
Calcified atherosclerotic plaques	34 (42%)	11 (22%)*	33 (40%)
Upper limbs claudication	4 (4.9%)	0 (0.0%)	1 (1.2%)

*Significant differences ($p < 0.05$); GCA, giant cell arteritis; PMR, polymyalgia rheumatica; SD, standard deviation.

GCA, PMR, and in controls. Receiver operating characteristic (ROC) curves for cut-off values of IMT depicting vasculitis are depicted in Figure 2. Cut-off values for IMT depicting vasculitis vs. controls are listed in Table 5.

The concordance correlation coefficient for intrarater reliability was 0.96 (95% CI 0.93–0.99), for interrater reliability was 0.96 (95% CI 0.93–0.98), and concordance for the GCA diagnosis was 100%.

Discussion

The diagnostics of large vessel GCA was improved by introducing new imaging techniques (7, 17–19). However, recommendations for extracranial arteries imaging have a much lower level of evidence compared with cranial arteries (2). IMT cut-off values were not used by the OMERACT group as a modality to define halo signs consistent with vasculitis due to lacking data (11). Defining ultrasound reference ranges could further improve the reproducibility and feasibility of this method.

Among arteries tested in our study, axillary and subclavian arteritis provided the best AUC for the diagnosis of GCA (Table 5), while CCA and axillary were most commonly involved (Table 4). It confirms previous experts' opinions (2, 6, 7) suggesting choosing the axillary artery for LV-GCA assessment. We demonstrated that CCA is the most commonly involved in GCA—a phenomenon that was proved in PET-CT studies but was hard to demonstrate in previous US studies probably due to a problem of differentiation with atherosclerosis that is frequent in this location (20). Axillary artery also demonstrated the lowest difference between highly specific and optimal cut-off values, a phenomenon possibly explained by a lower influence of atherosclerosis in axillary artery compared to arteries prone to develop atherosclerosis (carotid and femoral). However, we confirmed previous observations (21) that expanding the number of arteries examined may add to the diagnosis. In our study, this was the case with CCA (higher number of

TABLE 3 Factors potentially influencing intima-media thickness in GCA, isolated PMR, and controls.

	GCA ($N = 81$)			Isolated PMR ($N = 50$)			Non-GCA/PMR controls ($N = 83$)		
	Mean IMT ± SD (mm)	*p*	*R*	Mean IMT ± SD (mm)	*p*	*R*	Mean IMT ± SD (mm)	*p*	*R*
Female	0.73 ± 0.41	0.375	0.08	0.55 ± 0.20	0.009*	0.16	0.49 ± 0.15	<0.0005*	0.28
Male	0.80 ± 0.60			0.62 ± 0.21			0.61 ± 0.19		
Age < 68 years	0.74 ± 0.43	0.505	0.03	0.53 ± 0.17	0.035*	0.11	0.50 ± 0.16	<0.0005*	0.35
Age ≥ 68 years	0.77 ± 0.52			0.59 ± 0.22			0.59 ± 0.17		
Hypertension	0.75 ± 0.48	0.675	0.03	0.56 ± 0.20	0.536	0.04	0.56 ± 0.18	0.001*	0.19
No hypertension	0.77 ± 0.50			0.58 ± 0.21			0.50 ± 0.16		
Smoking	0.79 ± 0.56	0.288	0.08	0.59 ± 0.19	0.171	0.08	0.58 ± 0.20	0.017*	0.13
No smoking	0.73 ± 0.42			0.56 ± 0.21			0.52 ± 0.16		
Diabetes mellitus	0.75 ± 0.68	0.932	0.05	0.65 ± 0.30	0.089	0.10	0.54 ± 0.16	0.570	0.02
No diabetes	0.76 ± 0.45			0.56 ± 0.19			0.53 ± 0.18		
Hypercholesterolemia**	0.81 ± 0.59	0.035*	0.13	0.65 ± 0.22	0.009*	0.15	0.54 ± 0.15	0.854	0.03
No hypercholesterolemia	0.71 ± 0.40			0.56 ± 0.21			0.55 ± 0.17		
Calcified atherosclerotic plaques***	0.82 ± 0.58	0.015*	0.15	0.68 ± 0.27	<0.0005*	0.20	0.62 ± 0.20	<0.0005*	0.37
No calcified atherosclerotic plaques	0.72 ± 0.42			0.53 ± 0.16			0.48 ± 0.13		

IMT was calculated from measurements in all arteries (axillary, subclavian, superficial femoral, common carotid, and brachial), *p<0.05, **assessment limited to 99 patients and 33 controls, and ***calcified plaques covering >25% of the vessel lumen. GCA, giant cell arteritis; PMR, polymyalgia rheumatica; SD, standard deviation; R, Spearman's Rank Correlation Coefficient.

TABLE 4 Mean IMT in different affected large arteries in LV-GCA vs. cranial GCA with no LV-GCA, isolated PMR, and controls.

Artery	LV-GCA mean IMT ± SD, mm (#)	Cranial GCA with no LV-GCA mean IMT ± SD, mm ($N = 38$)	Isolated PMR mean IMT ± SD, mm ($N = 50$)	Non-GCA/PMR controls mean IMT ± SD, mm ($N = 83$)
Brachial	0.74* ± 0.33 (8)	0.40 ± 0.11	0.39 ± 0.13	0.37 ± 0.10
Axillary	1.42* ± 0.58 (23)	0.55 ± 0.15	0.53 ± 0.19	0.51 ± 0.15
Subclavian	1.31* ± 0.51 (18)	0.50 ± 0.11	0.50 ± 0.14	0.49 ± 0.15
Common carotid	1.13* ± 0.43 (24)	0.68 ± 0.17	0.61 ± 0.17	0.57 ± 0.18
Superficial femoral	1.90* ± 1.20 (11)	0.54 ± 0.17	0.54 ± 0.23	0.50 ± 0.15

#Number of patients with vasculitis. Significant findings are marked with asterisks: *p < 0.05 vs. all other groups. IMT, intima-media thickness; LV-GCA, large vessel giant cell arteritis; PMR, polymyalgia rheumatica; SD, standard deviation.

TABLE 5 Cut-off values for IMT depicting vasculitis in patients with GCA vs. controls.

Artery	AUC	Optimal IMT cut-off to diagnose GCA			IMT cut-off for 100% specificity to diagnose GCA		
		IMT (mm)	Sens. (%)	Spec. (%)	IMT (mm)	Sens. (%)	Spec. (%)
Brachial	0.842	0.48	88	85	0.96	25	100
Axillary	0.969	0.81	87	94	1.06	62	100
Subclavian	0.974	0.66	100	84	1.35	38	100
Common carotid	0.910	0.73	92	79	1.27	22	100
Superficial femoral	0.958	0.92	91	97	1.55	60	100

The maximal IMT value from bilateral CDU measurements was chosen. AUC, area under the curve; sens., sensitivity; spec., specificity; GCA, giant cell arteritis.

vasculitis in CCA vs. axillary arteries) and brachial arteries (one case of untypical brachial artery involvement without axillary arteritis). In addition, assessing calcified atherosclerotic plaques in typical places supplies clinically practical information on the potential confounding of IMT results by atherosclerosis (mean IMT was higher in patients with calcified atherosclerotic plaques), which may reduce false positive GCA rates. In our large real-life group, IMT highly specific for vasculitis was higher compared to the previously proposed IMT cut-off values (7, 22). It may be explained by a large cohort and a substantial number

of controls with atherosclerosis (patients with atherosclerosis predisposing conditions such as RA were included in the control group and a significant number of patients were referred by neurologists typically with atherosclerosis-related stroke to exclude its vasculitis etiology).

We demonstrated that IMT values may discriminate between GCA and its mimics (Table 4); however, false positive ultrasound results can be found in several diseases (23). An ultrasonographer should consider not only IMT but also the location of the pathological change (11), its structure, and echogenicity, as well as the grade of general atherosclerosis that all add to the final diagnosis of LV-GCA. Importantly, applying cut-off values requires prior identification of atherosclerosis by an ultrasonographer. The methodological obligation in our study was the measurement in a place without atherosclerotic plaque. Interpretation of IMT significance might be enriched by considering the presence of generalized atherosclerosis. The utility of IMT to diagnose or exclude GCA may be low according to the applied cut-off value. Therefore, we proposed two different IMT cut-off values, one based on optimal sensitivity and specificity and the other one that provided 100% specificity in our group, however, with reduced sensitivity. With that approach, lower cut-off values provide a probability for diagnosis instead of a definite diagnosis and necessitate additional ultrasonographic features and a more watchful approach to diagnosing GCA.

Our results indicate that IMT cut-off should be used cautiously to diagnose vasculitis, especially in the case of the presence of atherosclerosis and risk factors of atherosclerosis. Although calcified atherosclerotic plaques were assessed in arterial bifurcations typical for atherosclerosis (to check for the presence of general atherosclerosis) and not at the site of IMT measurement, their presence was correlated with increased IMT both in patients with GCA and controls. Male sex, age $\geq$ 68, hypertension, and smoking were associated with increased IMT in controls. Of note, these conditions (except for calcified atherosclerotic plaques) did not significantly influence the increase of IMT in patients with GCA suggesting that primary IMT increase by vasculitis might have overcome traditional CV risk factors.

Significantly increased IMT of the left CCA in GCA compared with the right in our observation seems to be only explained by anatomical asymmetry (the left CCA emerges directly from the aortic arch, whereas the right from the brachiocephalic trunk). The difference in left-to-right involvement in LV-GCA has been previously encountered but is not highlighted phenomenon (20, 24, 25). An ultrasonographer may profit from that knowledge when considering CCA arteritis. Interestingly, our brief review of the Medline database performed in April 2022 using a combination of Takayasu, GCA, vasculitis, and "left common carotid artery" or "right common carotid artery" revealed more articles concerning left than right side vascular complications.

An additional secondary result showed a decreased number of calcified atherosclerotic plaques in patients with isolated PMR vs. controls (Table 2). It is interesting in the context of occasionally reported favorable CV outcomes in patients with PMR/GCA (26). However, it requires further studies as some studies reported increased subclinical vascular changes in PMR, even in the absence of vasculitis (27).

Limitations of this study were that non-GCA/PMR controls were younger vs. GCA. However, age did not influence IMT in patients with GCA. The general limitation of the CDU method is that the assessment of IMT remains observer dependent as the measurement in a place without atherosclerotic plaques requires prior categorization into atherosclerosis/non-atherosclerosis. The possible limitation of the ultrasound-based study is that the observer might be reluctant to classify CCA with slightly increased IMT as vasculitis because this artery is commonly involved in atherosclerosis (13). This location might be an even more common site of arteritis in GCA, as demonstrated by PET examinations (20), but it should be examined by ultrasound with caution to conclude on vasculitis at least until more studies on CCA vasculitis vs. atherosclerosis will be available. We believe that determining the grade of atherosclerosis by assessing the presence of typical plaques in the carotid bulb and femoral arteries is feasible, to gain more information on the nature of the increase of IMT in CCA. The limitation of the study includes a lack of data on patients' obesity.

The strengths of the study include real-life referrals, examination of multiple large arteries, which, to the best of our knowledge, were not vastly analyzed previously, thorough analysis of potential confounders, and excellent interrater reliability.

In conclusion, we proposed IMT cut-off values to assess the probability of the diagnosis of GCA. Applying cut-off values may be enriched by prior identification of confounding by atherosclerosis, age, gender, hypertension, and smoking. They performed best in axillary and subclavian arteritis but examination of the other arteries may add to the diagnosis of GCA.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Pomeranian Medical University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MM and JF performed the examinations and organized the database. MM wrote the manuscript. All authors contributed to the conception, design, analysis interpretation of the study, and manuscript revision, as well as read and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.1055524/full#supplementary-material

References

1. Czihal M, Piller A, Schroettle A, Kuhlencordt P, Bernau C, Schulze-Koops H, et al. Impact of cranial and axillary/subclavian artery involvement by color duplex sonography on response to treatment in giant cell arteritis. *J Vasc Surg.* (2015) 61:1285–91. doi: 10.1016/j.jvs.2014.12.045

2. Dejaco C, Ramiro S, Duftner C, Besson FL, Bley TA, Blockmans D, et al. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. *Ann Rheum Dis.* (2018) 77:636–43. doi: 10.1136/annrheumdis-2017-212649

3. Diamantopoulos AP, 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? *Rheumatology.* (2016) 55:66–70. doi: 10.1093/rheumatology/kev289

4. Aschwanden M, Daikeler T, Kesten F, Baldi T, Benz D, Tyndall A, et al. Temporal artery compression sign—a novel ultrasound finding for the diagnosis of giant cell arteritis. *Ultraschall Med.* (2013) 34:47–50. doi: 10.1055/s-0032-1312821

5. Ješe R, Rotar Ž, Tomšič M, Hočevar A. The cut-off values for the intima-media complex thickness assessed by colour doppler sonography in seven cranial and aortic arch arteries. *Rheumatology.* (2020) 18:keaa578. doi: 10.1093/rheumatology/keaa578

6. Czihal M, Schröttle A, Baustel K, Lottspeich C, Dechant C, Treitl KM, et al. B-mode sonography wall thickness assessment of the temporal and axillary arteries for the diagnosis of giant cell arteritis: a cohort study. *Clin Exp Rheumatol.* (2017) 35 (Suppl. 103):128–33.

7. Schäfer VS, Juche A, Ramiro S, Krause A, Schmidt WA. Ultrasound cut-off values for intima-media thickness of temporal, facial and axillary arteries in giant cell arteritis. *Rheumatology.* (2017) 56:1479–83. doi: 10.1093/rheumatology/kex143

8. Milchert M, Diamantopoulos A, Brzosko M. Atlas of ultrasound application in large vessel arteritis: giant cell arteritis and takayasu arteritis. In: *Szczecin: Wydawnictwo Pomorskiej Akademii Medycznej.* Szczecin: Wydawnictwo Pomorskiej Akademii Medycznej (2016). p. 1–155.

9. Sebastian A, Coath F, Innes S, Jackson J, van der Geest KSM, Dasgupta B. Role of the halo sign in the assessment of giant cell arteritis: a systematic review and meta-analysis. *Rheumatol Adv Pract.* (2021) 5:rkab059. doi: 10.1093/rap/rkab059

10. Luqmani R, Lee E, Singh S, Gillett M, Schmidt WA, 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. *Health Technol Assess.* (2016) 20:1–238. doi: 10.3310/hta20900

11. Chrysidis S, Duftner C, Dejaco C, Schäfer VS, Ramiro S, Carrara G, et al. Definitions and reliability assessment of elementary ultrasound lesions in giant cell arteritis: a study from the OMERACT large vessel vasculitis ultrasound working group. *RMD Open.* (2018) 4:e000598. doi: 10.1136/rmdopen-2017-000598

12. Milchert M, Brzosko M, Bull Haaversen A, Diamantopoulos AP. Correspondence to "Slope sign": a feature of large vessel vasculitis? *Ann Rheum Dis.* (2021) 80:e198. doi: 10.1136/annrheumdis-2019-216601

13. De Miguel E, Beltran LM, Monjo I, Deodati F, Schmidt WA, Garcia-Puig J. Atherosclerosis as a potential pitfall in the diagnosis of giant cell arteritis. *Rheumatology.* (2018) 57:318–21. doi: 10.1093/rheumatology/kex381

14. Milchert M, Fischer K, Flicinski J, Przepiera-Bedzak H, Brzosko M. Arteriosclerosis or vasculitis? Color duplex sonography in giant cell arteritis. *J Rheumatol.* (2012) 39:1898–9. doi: 10.3899/jrheum.120317

15. Hunder GG, Arend WP, Bloch DA, Calabrese LH, Fauci AS, Fries JF, et al. The American college of rheumatology 1990 criteria for the classification of vasculitis. Introduction. *Arthritis Rheum.* (1990) 33:1065–7. doi: 10.1002/art.1780330802

16. Dasgupta B, Cimmino MA, Maradit-Kremers H, Schmidt WA, Schirmer M, Salvarani C, et al. 2012 provisional classification criteria for polymyalgia rheumatica: a European league against rheumatism/American college of rheumatology collaborative initiative. *Ann Rheum Dis.* (2012) 71:484–92. doi: 10.1016/j.ymed.2012.09.009

17. 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) 40:219–27. doi: 10.1024/0301-1526/a000096

18. Ghinoi A, Pipitone N, Nicolini A, Boiardi L, Silingardi M, Germanò G, et al. Large-vessel involvement in recent-onset giant cell arteritis: a case-control colour-Doppler sonography study. *Rheumatology.* (2012) 51:730–4. doi: 10.1093/rheumatology/ker329

19. van der Geest KSM, Borg F, Kayani A, Paap D, Gondo P, Schmidt W, et al. Novel ultrasonographic halo score for giant cell arteritis: assessment of diagnostic accuracy and association with ocular ischaemia. *Ann Rheum Dis.* (2020) 79:393–9. doi: 10.1136/annrheumdis-2019-216343

20. Imfeld S, Aschwanden M, Rottenburger C, Schegk E, Berger CT, Staub D, et al. [18F]FDG positron emission tomography and ultrasound in the diagnosis of giant cell arteritis: congruent or complementary imaging methods? *Rheumatology.* (2020) 59:772–8. doi: 10.1093/rheumatology/kez362

21. Bull Haaversen AC, Brekke LK, Kermani TA, Molberg Ø, Diamantopoulos AP. Extended ultrasound examination identifies more large vessel involvement in patients with giant cell arteritis. *Rheumatology*. (2022) keac478. doi: 10.1093/rheumatology/keac478

22. López-Gloria K, Castrejón I, Nieto-González JC, Rodríguez-Merlos P, Serrano-Benavente B, González CM, et al. Ultrasound intima media thickness cut-off values for cranial and extracranial arteries in patients with suspected giant cell arteritis. *Front Med*. (2022) 9:981804. doi: 10.3389/fmed.2022.981804

23. Evangelatos G, Grivas A, Pappa M, Kouna K, Iliopoulos A, Fragoulis GE. Cranial giant cell arteritis mimickers: a masquerade to unveil. *Autoimmun Rev*. (2022) 21:103083. doi: 10.1016/j.autrev.2022.103083

24. Grayson PC, Maksimowicz-McKinnon K, Clark TM, Tomasson G, Cuthbertson D, Carette S, et al. Distribution of arterial lesions in takayasu's arteritis and giant cell arteritis. *Ann Rheum Dis*. (2012) 71:1329–34. doi: 10.1136/annrheumdis-2011-200795

25. Park BW, Park SJ, Park H, Hwang JC, Seo YW, Cho HR. Stenosis or occlusion of the right subclavian and common carotid arteries is more common than that of the innominate artery in takayasu arteritis. *Vasc Specialist Int*. (2015) 31:120–4. doi: 10.5758/vsi.2015.31.4.120

26. Udayakumar PD, Chandran AK, Crowson CS, Warrington KJ, Matteson EL. Cardiovascular risk and acute coronary syndrome in giant cell arteritis: a population-based retrospective cohort study. *Arthritis Care Res*. (2015) 67:396–402. doi: 10.1002/acr.22416

27. Scrivo R, Silvestri V, Ciciarello F, Sessa P, Rutigliano I, Sestili C, et al. An exploratory cross-sectional study of subclinical vascular damage in patients with polymyalgia rheumatica. Sci Rep (2020) 10:11407. doi: 10.1038/s41598-020-68215-8

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EDITED BY
Ryu Watanabe,
Osaka Metropolitan University, Japan

REVIEWED BY
Alojzija Hocevar,
University Medical Center Ljubljana, Slovenia
Hubert De Boysson,
Centre Hospitalier Universitaire de Caen, France
Marcin Milchert,
Pomeranian Medical University, Poland

*CORRESPONDENCE
Andreas P. Diamantopoulos
✉ adiamanteas@gmail.com

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Norwegian society of rheumatology recommendations on diagnosis and treatment of patients with giant cell arteritis

Anne Bull Haaversen[1], Lene Kristin Brekke[2], Gunnstein Bakland[3], Erik Rødevand[4], Geirmund Myklebust[5] and Andreas P. Diamantopoulos[6]*

[1]Department of Rheumatology, Martina Hansens Hospital, Bærum, Norway, [2]Department of Rheumatology, Hospital for Rheumatic Diseases, Haugesund, Norway, [3]Department of Rheumatology, University Hospital of Northern Norway, Tromsø, Norway, [4]Department of Rheumatology, St. Olav's University Hospital, Trondheim, Norway, [5]Department of Research, Hospital of Southern Norway, Kristiansand, Norway, [6]Department of Infectious Diseases, Division of Internal Medicine, Akershus University Hospital, Lørenskog, Norway

Objective: To provide clinical guidance to Norwegian Rheumatologists and other clinicians involved in diagnosing and treating patients with giant cell arteritis (GCA).

Methods: The available evidence in the field was reviewed, and the GCA working group wrote draft guidelines. These guidelines were discussed and revised according to standard procedures within the Norwegian Society of Rheumatology. The European Alliance of Associations for Rheumatology (EULAR) recommendations for imaging and treatment in large vessel vasculitis and the British Society for Rheumatology (BSR) guidelines for diagnostics and treatment in GCA informed the development of the current guidelines.

Results: A total of 13 recommendations were developed. Ultrasound is recommended as the primary diagnostic test. In patients with suspected GCA, treatment with high doses of Prednisolone (40–60 mg) should be initiated immediately. For patients with refractory disease or relapse, Methotrexate (MTX) should be used as the first-line adjunctive therapy, followed by tocilizumab (TCZ).

Conclusion: Norwegian recommendations for diagnostics and treatment to improve management and outcome in patients with GCA were developed.

KEYWORDS

giant cell arteritis (GCA), large vessel vasculitis, guidelines, diagnosis, treatment

Introduction

Background

Giant cell arteritis (GCA) is the most common systemic vasculitis in adults and has a spectrum of possible presentations (1, 2). The main subsets include isolated cranial arteritis (c-GCA), isolated large vessel vasculitis (LV-GCA), and coexisting cranial and large vessel vasculitis (mixed-GCA) (2). Polymyalgia rheumatica (PMR) and GCA are closely related, and some argue that PMR lies within the spectrum of GCA. However, these conditions may occur simultaneously or independently of each other (3–5).

Giant cell arteritis occurs almost exclusively in people older than 50 years of age, with a peak in onset between 70 and 80 years of age and with a female predominance (6, 7). The majority of epidemiological studies on GCA have investigated European or North American populations, and the highest incidence has been reported in Nordic countries or North-American people of Scandinavian descent (8). Data on GCA occurrence in Africa, Asia, the Middle East, South- and Latin America, and Oceania are sparse and suggest that the condition is less common in non-Caucasians.

The annual incidence rate for GCA in Norway was recently estimated to be 22.5 per 100,000 persons ≥50 years of age (7).

Giant cell arteritis' etiopathogenesis is not fully understood but is considered to involve a combination of genetic and environmental factors (9). Different compositions of genetic background may contribute to global differences. There is also evidence that lifestyle factors such as body mass index, glucose levels, and smoking may influence the risk of GCA (10–14).

TABLE 1 Clinical symptoms and findings and laboratory results in giant cell arteritis (GCA) patients.

Clinical symptoms	Clinical findings	Laboratory findings
New-onset headache, often in the temporal area. Jaw/tongue claudication. Acute visual symptoms (e.g., amaurosis fugax, acute visual loss, diplopia) Constitutional symptoms (e.g., weight loss >2 kg, fever, fatigue, night sweats, and dry cough). Polymyalgia symptoms Limb claudication	Tenderness/thickening of the temporal arteries with or without reduced pulsation. Scalp tenderness Bruits (particularly in the axilla). Reduced pulses/blood pressure of the upper limbs	Anemia Elevated CRP or ESR Thrombocythemia Elevated liver enzymes (ALP) Normal creatinine

Objectives of the guidelines

These recommendations aim to provide clinical guidance to Rheumatologists and other clinicians involved in diagnosing and treating GCA patients. The guidelines cover individuals older than 50 years of age suspected to have GCA. The guidelines aim to harmonize the diagnostic and treatment procedures across specialists and departments in the Norwegian Healthcare System.

Methods

The Norwegian GCA working group (the members are the authors of these guidelines) developed the recommendations by reviewing the available evidence and writing the draft guidelines. The draft guidelines were discussed and revised according to standard procedures within the Norwegian Society of Rheumatology.

The European Alliance of Associations for Rheumatology (EULAR) recommendations for imaging and treatment in large vessel vasculitis (15, 16) and The British Society for

TABLE 2 Ultrasonographic findings in giant cell arteritis (GCA) patients (33).

Vessels	Ultrasound
Cranial arteries	Halo sign: homogenous, hypoechoic wall thickening that is well delineated toward the luminal side that is visible both in longitudinal and transverse planes, most commonly concentric Compression sign: the thickened arterial wall remains visible upon compression due to vasculitic wall thickening in comparison to surrounding tissue
Large vessels Other findings	Most commonly concentric vessel wall thickening homogeneous, hypo- or isoechoic (increased Intima media thickness)' Atherosclerosis hypo-, iso- or hyperechoic, non-homogeneous and localized plaques seen mainly in the large vessels at bifurcations

TABLE 3 Threshold intima media thickness (IMT) values in ultrasound examination (34).

Examined artery	IMT threshold (in mm)
Common temporal	0.42
Frontal temporal	0.34
Parietal temporal	0.29
Facial artery	0.37
Axillary artery	1.0
Subclavian artery	1.0
Occipital artery	0.4
Vertebral artery	0.7
Common carotid	1.0

Rheumatology (BSR) guidelines for diagnostics and treatment in GCA (17) served as the basis to the development of current guidelines. As the American College of Rheumatology guidelines recommend the use of Tocilizumab very early in the treatment of GCA patients, which is not refunded by the Norwegian Health Authorities, we chose not to incorporate these guidelines in the Norwegian guidelines (18). Also, the evidence on diagnostics and treatment of GCA published after 2018 was reviewed and included in this work. The PubMed and a combination of the search terms Giant cell arteritis and treatment and/or diagnosis were used. The review of individual studies was restricted to randomized controlled studies or prospective observational studies with >50 participants. The guidelines were proposed, discussed, revised, and accepted by voting/reaching an agreement by the majority of the members of the working group and the professional council (in Norwegian: Fagrådet) of the Norwegian Society of Rheumatology. The method used to obtain consensus was voting among members during meetings of the working group.

The present guidelines are the foundation upon which clinical practice should be based. Guidelines, unlike some types of policies, are not mandatory. Individual patient circumstances may influence clinical decisions, and clinicians should work alongside patients to make care-based shared decisions. Thus, failure to adhere to these guidelines should not necessarily be considered negligent. These guidelines should not be used to limit access to other diagnostic or treatment options.

Results

Diagnosis

Recommendation 1

In patients with suspected GCA, a thorough history should be obtained, including inquiry about polymyalgia symptoms, new-onset headache, tongue- or jaw-claudication, vision disturbances, arm or leg claudication, constitutional symptoms (fatigue, fever, and weight loss). Additionally, a thorough clinical examination and laboratory workup should be performed including heart and lung auscultation, blood pressure in both arms, temperature, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and full blood count (**Table 1**).

Recommendation 2

Patients suspected of having GCA, should be directly referred to a Fast-Track Clinic (FTC) or a rheumatologist for further evaluation, treatment, and follow-up within 24 h. In cases where FTC- or rheumatology consult is unavailable within 24 h the patient may be referred to other relevant specialists (e.g., neurologist, ophthalmologist, and internist). FTC consists of an evaluation by ultrasound or other imaging modality which can confirm the diagnosis immediately (19). Diagnostic work-up should not delay the initiation of treatment.

TABLE 4 Histological findings in patients with giant cell arteritis (GCA) (35).

Histological features In GCA	
Location	All three arterial layers may be involved. In severe cases there is a diffuse widespread inflammatory infiltration Main inflammatory bulk is located in the adventitia media junction The inflammatory infiltrate has a concentric ring appearance, with the thicker ring adjacent to adventitia-media junction and the thinner ring in proximity to media-intima junction (transmural inflammation) The media is relatively spared The myofibroblastic proliferation of intima leads to occlusion of the lumen
Types of cells	CD-4+ lymphocytes and macrophages are the most commonly seen Giant cells are seen in 50–75% of cases and their absence do not preclude the diagnosis Plasma cells and eosinophils may also be seen; neutrophils are rarely present
Other histological patterns	
Periadventitial and adventitial inflammation	The inflammation in GCA spreads from adventitia to intima. Inflammation affecting only the periadventitial vessels, the vasa vasorum and the adventitial tissue may also be seen Cautious interpretation is needed taking into account clinical, laboratorial and imaging findings
Isolated intima inflammation	Rarely seen
Healed arteritis	Features of healed inflammation: irregular intima proliferation, changes in the internal elastic lamina, fibrosis and neovascularization of the media and adventitia in the absence of ongoing active inflammation Note that: These changes can also be seen as a result of normal aging (atherosclerosis)
Atherosclerosis	Regular intima proliferation with focal loss of the internal elastic lamina. Calcifications could be present
Fibrinoid necrosis	Rarely seen (Evaluate for other diagnoses, if clinical findings are not typical for GCA)

Recommendation 3

In patients with suspected GCA, ultrasound of at least temporal and axillary arteries (20) should be performed by an ultrasonographer experienced in vascular ultrasound using high-end ultrasound equipment (21) (**Tables 2**, **3**). Ultrasound of the facial artery further increases the sensitivity to diagnose

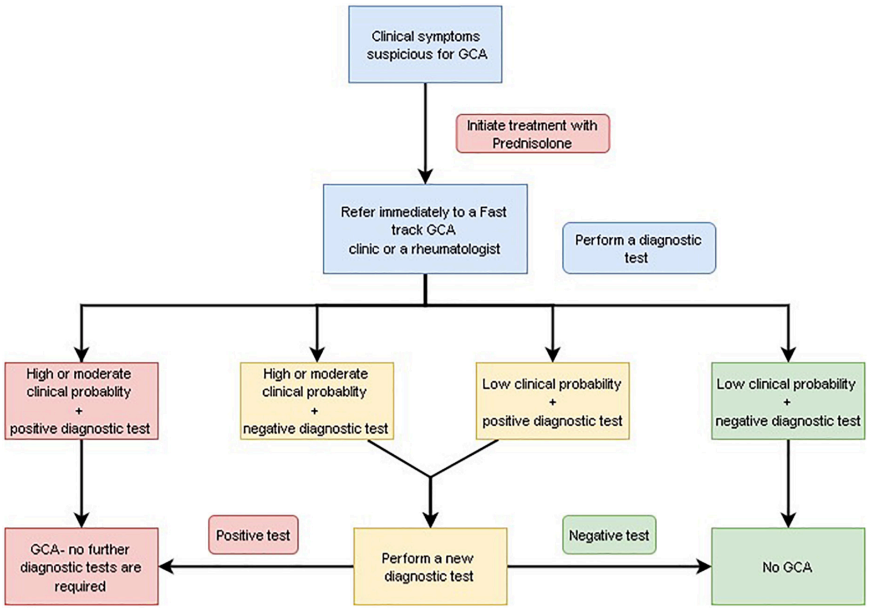

FIGURE 1
Diagnostic algorithm for giant cell arteritis (GCA).

TABLE 5 Summary of the Norwegian society of rheumatology's recommendations on diagnosis and treatment of patients with giant cell arteritis (GCA).

# of recommendation	
1	Refer patients suspected of having GCA to a Fast-Track GCA clinic (19) or a rheumatologist within 24 h. Treatment should not be delayed while waiting for this evaluation.
2	Obtain a thorough history and perform clinical examination and laboratory work up.
3	In patients with high clinical suspicion of GCA and a positive diagnostic test (temporal artery biopsy or any imaging modality) no further test is required to confirm the diagnosis.
4	Perform ultrasound of temporal and axillary arteries using high-end ultrasound equipment. Ultrasound of facial artery increases the sensitivity (32). If ultrasound is not available or inconclusive, perform another diagnostic test.
5	Refer to ophthalmologist if visual manifestations.
6	Initiate treatment with 40 mg Prednisolone/day in patients without visual manifestations. Initiate treatment with Prednisolone 60 mg/day if visual manifestations are present, consider a single dose of 500 mg IV methylprednisolone.
7	Taper daily Prednisolone dose as described in **Table 6**.
8	In minor relapse: Increase Prednisolone dose to the most recent effective dosage. In refractory disease or major relapse: Initiate Methotrexate (MTX) 20 mg/week sc. Consider Tocilizumab (TCZ) 162 mg/week sc if the patient is not tolerating or has a refractory or relapsing disease while on MTX.
9	Patients with GCA and high risk for osteoporosis should receive treatment according to the Norwegian guidelines for osteoporosis diagnostics and treatment.
10	Acetylsalicylic acid should not be used routinely, and should be considered on individual indication.
11	A relapse should be confirmed by an imaging modality. Modified Kerr's (NIH criteria) could be used to monitor disease activity (31).
12	Reevaluate the diagnosis in patients not responding to standard treatment.
13	Follow-up should be performed every month until remission is achieved, and then after 3 months, 6 months, and yearly.

GCA (20). If ultrasound is not available or inconclusive, a biopsy of the temporal artery should be considered. The length of the biopsy should be >1 cm after fixation. Giant cells in the biopsy are not obligate for the diagnosis of GCA, but appropriate pathological findings should be present (**Table 4**). Alternatively, Magnetic Resonance Angiography (MRA) of temporal arteries or Positron Emission Tomography (PET-CT) may be performed. In addition, ultrasound of large vessels (carotid, vertebral, and subclavian) (22) or CT of large vessels or MRA or PET-CT depending on the availability is recommended. It is essential to recognize the disease extent as early as possible as large vessel involvement may indicate difficult-to-treat disease, while temporal artery involvement has been associated with a higher risk for visual loss (23, 24). The choice of imaging modality depends on the local availability.

Recommendation 4

In a patient with high clinical suspicion of GCA and a positive diagnostic test (biopsy or imaging modality), no further test is required to confirm the diagnosis. In patients with low clinical suspicion of GCA and a negative diagnostic test (biopsy or imaging modality), the probability for GCA is low. In other cases, an individual assessment will be necessary for further diagnostics.

Recommendation 5

In patients with GCA and visual symptoms, referral to an ophthalmologist is highly recommended. Initiation of treatment should not be delayed while waiting for this evaluation (**Figure 1** and **Table 5**).

Treatment

Recommendation 6

In patients with suspected GCA, glucocorticoids should be immediately initiated. The diagnostic work-up should not delay the initiation of treatment. For patients without visual manifestations we recommend a starting dose of 40 mg Prednisolone/day. In patients with visual involvement (visual loss, diplopia, amaurosis fugax, and blurred vision), we recommend starting with 60 mg Prednisolone/day. A single dose of 500 mg × 1 methylprednisolone iv followed by Prednisolone 60 mg/day may be individually considered, but the evidence is sparse (25–27).

Recommendation 7

In patients with GCA, Prednisolone should be tapered by 5 mg every 2nd week till 20 mg/day, after that with 2.5 mg every 3rd week till 10 mg/day, and after that with 1.25 mg every 3rd week to 5 mg/day. We recommend continuing treatment with 5 mg/day at least for 1 year after initiation of Prednisolone. Further tapering can be considered on an individual basis if the patient has been in remission for at least 1 year. When starting with dose 60 mg/day, Prednisolone should be tapered by 10 mg every week till 40 mg/day, thereafter tapering as described above (**Table 6**).

Recommendation 8

If the patients suffers a relapse, we recommend an increase in Prednisolone dose to the last effective dose, or a higher dose based on the severity of the relapse and an individual assessment. In patients with refractory disease or a major

TABLE 6 Prednisolone tapering.

Weeks	Prednisolone dose (mg)	
1	60	Starting dose when visual manifestations
2	50	
3 + 4	40	Starting dose when no visual manifestations
5 + 6	35	
7 + 8	30	
9 + 10	25	
11 + 12	20	
13 + 14 + 15	17.5	
16 + 17 + 18	15	
19 + 20 + 21	12.5	
22 + 23 + 24	10	
25 + 26 + 27	8.75	
28 + 29 + 30	7.5	
31 + 32 + 33	6.25	
34–52	5	

TABLE 7 Definitions of disease activity (16).

Major relapse	Recurrence of active disease with either of the following: a. Clinical features of ischemia (jaw claudication, visual symptoms, visual loss attributable to GCA, scalp necrosis, stroke, limb claudication) b. Evidence of active aortic inflammation resulting in progressive aortic or large vessel dilatation, stenosis, or dissection
Minor relapse	All patients suffering a relapse without the characteristics of a major relapse (constitutional symptoms, polymyalgia, and headache)
Refractory disease	Active disease despite the use of standard care therapy
Remission	Absence of all clinical signs and symptoms attributable to active GCA Normalization of ESR and CRP No evidence of progressive vessel narrowing or dilatation for patients with large vessel involvement

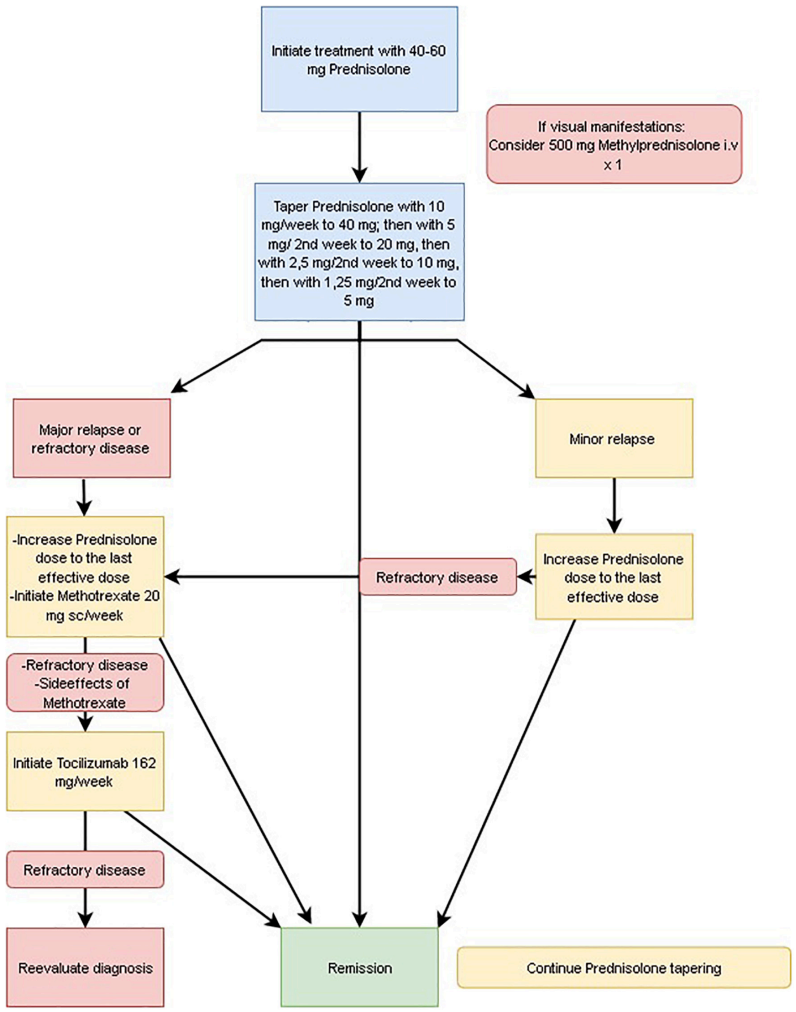

FIGURE 2
Treatment algorithm for giant cell arteritis (GCA).

relapse (Table 7), initiation of Methotrexate (MTX), preferably subcutaneously, 20 mg/week, should be considered. The dose should be adjusted according to the patient's age and kidney function. Tocilizumab (TCZ) 162 mg/week sc should be considered if the patient is not tolerating MTX or suffer a relapse while on MTX (according to the Norwegian Tender System). Leflunomide or Azathioprine may be considered, but evidence supporting their use is scarce. There is currently no robust evidence supporting the use of TNF-α inhibitors or other biologics than TCZ in patients with GCA.

TABLE 8 Modified Kerr's criteria: >1 point indicates active disease (31).

Elevated CRP or ESR not attributed to other causes than vasculitis	+1
Clinical symptoms of ischemia (headache and jaw claudication) not attributed to other causes than vasculitis	+1
Constitutional symptoms (fatigue, fever, weight loss, and polymyalgia symptoms) not attributed to other causes than vasculitis	+1
Findings suggesting active vasculitis in an imaging modality: Involvement of new vascular areas Increasing IMT in already involved areas	+1

Recommendation 9

Giant cell arteritis patients with new-onset disease should be referred to a measurement of bone mass density. In patients with GCA and high risk for osteoporosis, treatment according to the Norwegian guidelines for osteoporosis should be initiated (28).

Recommendation 10

In patients with GCA, we do not routinely recommend using Acetylsalicylic acid unless cardiovascular reasons support its use (Figure 2).

Follow up

Recommendation 11

In GCA patients, follow-up should be continued every month until remission is achieved. Thereafter follow-up at 3 months, 6 months, and thereafter yearly.

Recommendation 12

In GCA patients who suffer a relapse, the relapse should, if possible, be confirmed by an imaging modality, preferably ultrasound, and/or laboratory tests (29, 30). Modified Kerr's (NIH) criteria (originally developed for Takayasu arteritis) may be used to monitor disease activity (31) (**Tables 7**, **8**).

Recommendation 13

In GCA patients with relapsing or refractory disease, alternative diagnoses should be considered (e.g., malignancy, autoinflammatory syndromes).

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

AH prepared the manuscript. AD, LB, GB, GM, and ER contributed equally to the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Weyand CM, Goronzy JJ. Medium- and large-vessel vasculitis. *N Engl J Med.* (2003) 349:160–9.

2. 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. *Rheumatology.* (2017) 56:506–15. doi: 10.1093/rheumatology/kew273

3. Weyand CM, Goronzy JJ. Clinical practice. Giant-cell arteritis and polymyalgia rheumatica. *N Engl J Med.* (2014) 371:50–7.

4. Schmidt J, Warrington KJ. Polymyalgia rheumatica and giant cell arteritis in older patients: diagnosis and pharmacological management. *Drugs Aging.* (2011) 28:651–66.

5. Cantini F, Niccoli L, Storri L, Nannini C, Olivieri I, Padula A, et al. Are polymyalgia rheumatica and giant cell arteritis the same disease? *Semin Arthritis Rheum.* (2004) 33:294–301.

6. Myklebust G, Gran JT. A prospective study of 287 patients with polymyalgia rheumatica and temporal arteritis: clinical and laboratory manifestations at onset of disease and at the time of diagnosis. *Br J Rheumatol.* (1996) 35:1161–8. doi: 10.1093/rheumatology/35.11.1161

7. Brekke LK, Diamantopoulos AP, Fevang BT, Abetamus J, Espero E, Gjesdal CG. Incidence of giant cell arteritis in Western Norway 1972-2012: a retrospective cohort study. *Arthritis Res Ther.* (2017) 19:278.

8. Sharma A, Mohammad AJ, Turesson C. Incidence and prevalence of giant cell arteritis and polymyalgia rheumatica: a systematic literature review. *Semin Arthritis Rheum.* (2020) 50:1040–8. doi: 10.1016/j.semarthrit.2020.07.005

9. Weyand CM, Goronzy JJ. Immune mechanisms in medium and large-vessel vasculitis. *Nat Rev Rheumatol.* (2013) 9:731–40. doi: 10.1038/nrrheum.2013.161

10. Tomasson G, Bjornsson J, Zhang Y, Gudnason V, Merkel PA. Cardiovascular risk factors and incident giant cell arteritis: a population-based cohort study. *Scand J Rheumatol.* (2019) 48:213–7. doi: 10.1080/03009742.2018.1506821

11. Ungprasert P, Thongprayoon C, Warrington KJ. Lower body mass index is associated with a higher risk of giant cell arteritis: a systematic review and meta-analysis. *Ann Transl Med.* (2015) 3:232. doi: 10.3978/j.issn.2305-5839.2015.09.31

12. Jakobsson K, Jacobsson L, Warrington K, Matteson EL, Liang K, Melander O, et al. Body mass index and the risk of giant cell arteritis: results from a prospective study. *Rheumatology.* (2015) 54:433–40. doi: 10.1093/rheumatology/keu331

13. Brennan DN, Ungprasert P, Warrington KJ, Koster MJ. Smoking as a risk factor for giant cell arteritis: a systematic review and meta-analysis. *Semin Arthritis Rheum.* (2018) 48:529–37. doi: 10.1016/j.semarthrit.2018.07.001

14. Wadstrom K, Jacobsson L, Mohammad AJ, Warrington KJ, Matteson EL, Turesson C. Negative associations for fasting blood glucose, cholesterol and triglyceride levels with the development of giant cell arteritis. *Rheumatology.* (2020) 59:3229–36. doi: 10.1093/rheumatology/keaa080

15. Dejaco C, Ramiro S, Duftner C, Besson FL, Bley TA, Blockmans D, et al. EULAR recommendations for the use of imaging in large vessel vasculitis in clinical practice. *Ann Rheum Dis.* (2018) 77:636–43. doi: 10.1136/annrheumdis-2017-212649

16. Hellmich B, Agueda A, Monti S, Buttgereit F, de Boysson H, Brouwer E, et al. 2018 Update of the EULAR recommendations for the management of large vessel vasculitis. *Ann Rheum Dis.* (2020) 79:19–30.

17. Mackie SL, Dejaco C, Appenzeller S, Camellino D, Duftner C, Gonzalez-Chiappe S, et al. British Society for Rheumatology guideline on diagnosis and treatment of giant cell arteritis. *Rheumatology.* (2020) 59:E1–23.

18. Maz M, Chung SA, Abril A, Langford CA, Gorelik M, Guyatt G, et al. 2021 American college of rheumatology/vasculitis foundation guideline for the management of giant cell arteritis and takayasu arteritis. *Arthritis Care Res.* (2021) 73:1071–87. doi: 10.1002/acr.24632

19. Diamantopoulos AP, 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? *Rheumatology*. (2015) 55:66–70. doi: 10.1093/rheumatology/kev289

20. Jese R, Rotar Z, Tomsic M, Hocevar A. The cut-off values for the intima-media complex thickness assessed by colour Doppler sonography in seven cranial and aortic arch arteries. *Rheumatology*. (2021) 60:1346–52. doi: 10.1093/rheumatology/keaa578

21. Chrysidis S, Terslev L, Christensen R, Fredberg U, Larsen K, Lorenzen T, et al. Vascular ultrasound for the diagnosis of giant cell arteritis: a reliability and agreement study based on a standardised training programme. *RMD Open*. (2020) 6:e001337. doi: 10.1136/rmdopen-2020-001337

22. Bull Haaversen AC, Brekke LK, Kermani TA, Molberg O, Diamantopoulos AP. Extended ultrasound examination identifies more large vessel involvement in patients with giant cell arteritis. *Rheumatology*. (2022) [Online ahead of print].. doi: 10.1093/rheumatology/keac478

23. Hocevar A, Rotar Z, Jese R, Semrl SS, Pizem J, Hawlina M, et al. Do early diagnosis and glucocorticoid treatment decrease the risk of permanent visual loss and early relapses in giant cell arteritis: a prospective longitudinal study. *Medicine*. (2016) 95:e3210. doi: 10.1097/MD.0000000000003210

24. Muratore F, Kermani TA, Crowson CS, Green AB, Salvarani C, Matteson EL, et al. Large-vessel giant cell arteritis: a cohort study. *Rheumatology*. (2015) 54:463–70. doi: 10.1093/rheumatology/keu329

25. Chan CC, Paine M, O'Day J. Steroid management in giant cell arteritis. *Br J Ophthalmol*. (2001) 85:1061–4. doi: 10.1136/bjo.85.9.1061

26. Hayreh SS, Zimmerman B, Kardon RH. Visual improvement with corticosteroid therapy in giant cell arteritis. Report of a large study and review of literature. *Acta Ophthalmol Scand*. (2002) 80:355–67. doi: 10.1034/j.1600-0420.2002.800403.x

27. Hayreh SS, Biousse V. Treatment of acute visual loss in giant cell arteritis: should we prescribe high-dose intravenous steroids or just oral steroids? *J Neuroophthalmol*. (2012) 32:278–87. doi: 10.1097/WNO.0b013e3182688218

28. Rheumatology. *Osteoporosis*. (2021). Available online at: https://metodebok.no/index.php?action=topic&item=AtEEtJ7q (accessed May 01, 2022).

29. Ponte C, Monti S, Scire CA, Delvino P, Khmelinskii N, Milanesi A, et al. Ultrasound halo sign as a potential monitoring tool for patients with giant cell arteritis: a prospective analysis. *Ann Rheum Dis*. (2021) 80:1475–82. doi: 10.1136/annrheumdis-2021-220306

30. Seitz L, Christ L, Lotscher F, Scholz G, Sarbu AC, Butikofer L, et al. Quantitative ultrasound to monitor the vascular response to tocilizumab in giant cell arteritis. *Rheumatology (Oxford)*. (2021) 60:5052–9. doi: 10.1093/rheumatology/keab484

31. Kerr GS, Hallahan CW, Giordano J, Leavitt RY, Fauci AS, Rottem M, et al. Takayasu arteritis. *Ann Intern Med*. (1994) 120:919–29.

32. Jese R, Rotar Z, Tomsic M, Hocevar A. The role of colour doppler ultrasonography of facial and occipital arteries in patients with giant cell arteritis: a prospective study. *Eur J Radiol*. (2017) 95:9–12. doi: 10.1016/j.ejrad.2017.07.007

33. Chrysidis S, Duftner C, Dejaco C, Schafer VS, Ramiro S, Carrara G, et al. Definitions and reliability assessment of elementary ultrasound lesions in giant cell arteritis: a study from the OMERACT Large Vessel Vasculitis Ultrasound Working Group. *RMD Open*. (2018) 4:e000598. doi: 10.1136/rmdopen-2017-000598

34. Andel PM, Chrysidis S, Geiger J, Haaversen A, Haugeberg G, Myklebust G, et al. Diagnosing giant cell arteritis: a comprehensive practical guide for the practicing rheumatologist. *Rheumatology*. (2021) 60:4958–71. doi: 10.1093/rheumatology/keab547

35. Stamatis P. *Clinical and Epidemiological Studies on Giant Cell Arteritis*. Lund: Lund University (2021).

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