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Review

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The value of ultrasound for monitoring disease activity in giant cell arteritis

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Abstract

Giant cell arteritis (GCA) is the most common primary systemic vasculitis in the elderly. Although the diagnosis of GCA has improved, monitoring its disease activity remains challenging due to the lack of validated tools and biomarkers. The current reliance on assessing symptoms, physical signs, and inflammatory markers during disease follow-up presents limitations, notably the nonspecific nature of GCA-related symptoms and the suppressive impact of IL-6 inhibitors on inflammatory markers. Therefore, recent attention has shifted toward acknowledging imaging as a monitoring tool, particularly ultrasound, given its widespread accessibility, cost-effectiveness, and well-established role in GCA diagnosis. Research on this topic has found that ultrasound characteristics, including the number of affected arterial segments and halo size, are associated with laboratory markers and treatment response, underscoring the ultrasound's potential as a monitoring tool for GCA. It has also been demonstrated that ultrasound abnormalities progress differently throughout the disease course, depending on the type of arterial involvement, with vessel wall changes in the axillary arteries resolving more slowly than those in the temporal arteries. Nevertheless, there are still no studies comparing the added value of regular ultrasounds for monitoring disease activity to clinical and laboratory monitoring alone; hence, this imaging modality is not yet recommended for patients with GCA in clinical and biochemical remission. This narrative review aims to synthesize the main research findings of key studies addressing the role of ultrasound for monitoring disease activity in GCA, with a focus on the pattern of arterial involvement. It highlights the potential of ultrasound, particularly halo sign assessment, for evaluating disease progression but notes that further validation and standardization of protocols are needed to improve accuracy and enable routine use.

Keywords: Ultrasound, monitor, giant cell arteritis, follow-up

INTRODUCTION

Giant cell arteritis (GCA) is the most common form of primary systemic vasculitis in adults, affecting large- and medium-sized arteries, in particular the aorta and its main branches[1]. Visual loss is one of the most feared complications in patients with cranial artery involvement, often manifesting early in the disease course[2]. Thus, extensive research has been undertaken to identify the most efficient and accurate method for diagnosing these patients, enabling a high level of diagnostic certainty before initiating a treatment plan that often involves at least one year of immunosuppression, including prolonged use of glucocorticoids (GCs).

Currently, ultrasound of the temporal (TA) and axillary (AX) arteries is the first imaging modality recommended to assess patients with suspected GCA[3]. Once the diagnosis of GCA is established, correct monitoring of disease activity is essential. However, there are still no validated tools or biomarkers to assess response to therapy in GCA[4]. In routine care, the follow-up evaluation of patients with GCA typically relies on assessing GCA-related symptoms and vascular abnormalities on physical examination, as well as monitoring laboratory markers, in particular C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). Approximately half of patients with GCA experience relapse during their disease course, requiring treatment adjustments[5,6]. These relapses are usually characterized by a worsening of disease-related symptoms and increased inflammatory markers[7]. However, symptoms of GCA can be mild and nonspecific, and inflammatory markers do not reliably indicate disease activity, are not GCA-specific, and their production is suppressed in patients treated with tocilizumab, an IL-6 inhibitor approved for GCA treatment[8-12].

Therefore, given the evident limitations of a monitoring approach based solely on the assessment of clinical signs, symptoms and laboratory markers, in recent years, imaging techniques have emerged as promising tools for evaluating patients with GCA, with ultrasound being particularly notable due to its high accessibility and low cost[13-25]. The inflammatory infiltration of the artery wall results in homogenous, hypoechoic wall thickening, defined as the 'halo' sign, which is considered the most important ultrasound finding to establish the diagnosis of GCA[26]. In addition, various studies have suggested different cut-off values for the intima-media thickness (IMT) to identify the presence of a positive halo sign: 0.3-1.0 mm for temporal arteries[25,27-30] and 1.0-2.0 mm for axillary arteries[28,30-32]. However, our understanding of the association between disease activity and the characteristics of the halo sign, namely its IMT, remains limited. In addition, it is yet to be accurately determined how the halo sign behaves over time according to the pattern of vasculitic involvement at baseline (i.e., cranial *vs.* extracranial large vessel involvement).

This narrative review aims to provide a comprehensive summary of the main research findings regarding the role of ultrasound in monitoring disease activity in GCA. It focuses on how disease activity may affect vessel wall changes detected by ultrasound and explores variations across different types of arterial segments. It also identifies existing research gaps and outlines a future research agenda. The main characteristics of the studies included are summarized in Table 1.

ULTRASOUND FOR MONITORING DISEASE ACTIVITY

Cranial arteries

Giant cell arteritis primarily targets cranial arteries, with the TA being the most frequently affected vessel. Studies assessing the TA by ultrasound during disease course have been conducted[13,25]. Pérez López *et al.* prospectively assessed 22 patients (18 with GCA and 4 with PMR) at 6 months who presented with a TA halo sign on ultrasound at disease onset[13]. The halo sign was reported to persist in 10/18 (55.6%) patients

Table 1. Key findings from the main studies on the use of ultrasound for monitoring giant cell arteritis

Authors, year	Study design	N patients assessed	Arteries assessed	Time points of ultrasound	Settings - probes used	Main conclusion
Assessment of the cranial arteries						
Pérez López *et al.*, 2009[13]	Prospective cohort	22	TA	Baseline, 6 weeks, 6 months	Linear 5-10 MHz (Aplio-80, Toshiba)	6 weeks: 11/22 patients had persistent halo sign 6 months: 10/18 patients had persistent halo sign (all in clinical remission)
De Miguel *et al.*, 2012[25]	Prospective cohort	30	TA	Every 2 weeks (1st month), then every 4 weeks until halo disappearance	9-14 MHz (LOGIQ-9, GE)	94.7% of patients had halo resolution during follow-up Mean time until halo disappearance: 9 ± 7 weeks for relapsing GCA and 11 ± 7 weeks for new-onset GCA More branches with halo required a longer time for halo disappearance Higher mean CRP and ESR observed in patients with halo at baseline and during relapse *vs.* at the time of halo disappearance
Assessment of the extracranial arteries						
Schmidt *et al.*, 2008[34]	Prospective cohort	40	AX, SC, brachial	Baseline, no fixed time points	NP	Halo sign disappeared in 30%, decreased in 53%, unchanged in 8%, worsened in 5% and became occluded in 5% after a mean follow-up of 39 ± 22 months No ischemic arm complications were reported during follow-up
Czihal *et al.*, 2013[22]	Retrospective, cross-sectional	34	AX, SC, brachial	Baseline, at least after 6 months (no fixed time points)	NP	32.4% of patients had complete halo disappearance after a mean follow-up of 22 ± 17 months Right AX IMT decreased from a mean of 1.8 ± 0.7 to 1.3 ± 0.4 mm; left AX IMT from a mean of 1.7 ± 0.8 mm to 1.2 ± 0.4 mm (assessed in 17 patients) Relief of symptoms was associated with lower ESR at diagnosis [47 (11) *vs.* 75 (32) mm/h; $P = 0.02$] and less presence of anemia (0% *vs.* 82%; $P < 0.01$) and SC involvement (20% *vs.* 82%; $P = 0.04$) No new ischemic symptoms of the upper limbs were reported during follow-up
Bosch *et al.*, 2021[18]	Retrospective and prospective cohort	73	AX	Baseline, several follow-up visits (no fixed time points)	Type of probe NP (MyLab Twice eHD or MyLab 70, Esaote)	AX IMT declined in the first 18 months by -0.5 mm (range -2.77 to 0.50) Median AX IMT after a median disease duration of 48 months (16-137) was 0.90 mm (0.46-2.20) AX IMT of 0.87 mm was highly specific (specificity 96%, sensitivity 61%) for diagnosis of chronic AX GCA
Assessment of the cranial and extracranial arteries						
Aschwanden *et al.*, 2010[35]	Prospective cohort	9	TA, AX, SC, carotid, vertebral, femoral, popliteal	Baseline, 6 months	Linear 3-9 and 5-17 MHz (iU22, Philips)	6 months: 76/84 vascular segments had persistent vasculitis, with no systemic inflammation; new vasculitic lesions occurred in one patient at two segments
Monti *et al.*, 2018[21]	Retrospective cohort	167	TA, AX	Baseline, several follow-up visits (no fixed time points)	TA: L8-i18 MHz linear hockey stick AX: ML6-15 MHz linear matrix array (LOGIQ-E9, GE)	New-onset GCA had more frequently ≥ 4 segments with halo sign *vs.* relapsing GCA (39% *vs.* 7.7%, $P = 0.008$) Mean AX IMT was higher in the new-onset GCA group compared to the relapsing group (1.6 ± 0.4 *vs.* 1.4 ± 0.2 mm, $P = 0.02$); no difference was found for the TA IMT (0.6 ± 0.2 *vs.* 0.6 ± 0.1 mm, $P > 0.05$)

Aschwanden *et al.*, 2019[17]	Prospective cohort	42	TA, AX, SC, carotid, vertebral, femoral, popliteal	Baseline, 6, 12 and 24 months	Linear 3-9 and 5-17 MHz (iU22, Philips) or Linear 12-3 and 18-5 MHz (EPIQ 7 duplex, Philips)	TA: 22/26 (85%) cases showed a reduction in wall thickening (11/26 with complete normalization); 4/26 no improvement (2/26 with new vessel wall thickening) LV: 19/42 (45%) cases showed a reduction in wall thickening (1/42 with complete normalization); 23/42 with no improvement (3/42 with new vessel wall thickening) No differences between cumulative GC dose, use of DMARDs, and number of relapses were reported between patients with or without wall thickness reduction (TA or LV) during follow-up
Ford *et al.*, 2020[15]	Retrospective	42	TA, AX, SC	Baseline, several follow-up visits (no fixed time points)	L8-i18 MHz linear hockey stick (TA > 15 and AX/SC < 15 MHz) (LOGIQ S8 and E9, GE)	42 patients (36 with active vasculitis and 6 with hyperechoic wall thickening at baseline ultrasound) were followed for a median time of 5.1 (IQR 2.6-7.9) months At follow-up ultrasound: 15/36 had no arteritis, 12/36 a hyperechoic wall thickening and 9/36 still had active arteritis; 3/6 had no arteritis, 1/6 active arteritis and 2/6 still had hyperechoic wall thickening AX ultrasound abnormalities had slower improvement compared to TA
Sebastian *et al.*, 2020[36]	Prospective cohort	21	TA, AX	Baseline (pre TCZ), follow-up visit within a range of 3-12 months (post TCZ)	Linear LA435 (6-18 MHz) (MyLab Twice, Esaote)	38/54 arterial segments showed a decrease in IMT following the initiation of TCZ The TA Halo Score showed a marked improvement upon follow-up; the AX Halo Score remained stable
Ponte *et al.*, 2020[20]	Cross-sectional	121	TA, AX	Single ultrasound assessment within 7 days of GC initiation	NP (different probes with B-mode frequencies ≥ 10 MHz)	Maximum TA halo IMT: consistent reduction over 7 days of GCs (r = -0.30, P = 0.001); significant difference in halo IMT between patients assessed on day 0 and ≥ 4 days of GCs (P < 0.003) [n = 112 patients] Sum of all TA halo IMT: consistent reduction over 7 days of GCs (r = -0.23, P < 0.001); significant difference in sum of halo IMT between patients assessed on day 0 and ≥ 4 days of GCs (P < 0.003) [n = 395 TA halos] Maximum AX halo IMT: no correlation was found between halo size and number of days on GCs within 7 days of treatment (r = -0.064, P = 0.721) [n = 33 patients] Sum of all AX halo IMT: no correlation was found between halo size and number of days on GCs within 7 days of treatment (r = -0.044, P = 0.764) [n = 44 AX halos]
Ponte *et al.*, 2021[19]	Prospective cohort	49	TA, AX	Baseline, weeks 1, 3, 6, 12 and 24	L8-i18 MHz linear hockey stick (LOGIQ-E9, GE) - Portugal and Linear 6-18 MHz (MyLab 7, Esaote) - Italy	TA halo features (number of segments with halo and sum and maximum halo IMT) showed significant standardized mean difference between baseline and all time points AX halo features (sum and maximum halo IMT) showed significant standardized mean difference between baseline and only week 6 onward The number of TA segments with halo and sum and maximum TA halo IMT demonstrated a significant correlation with ESR (0.41, 0.44 and 0.48), CRP (0.34, 0.39 and 0.41), BVAS (0.29, 0.36 and 0.35), and GC cumulative dose (-0.34, -0.37 and -0.32); no significant correlation was observed for the AX halo features Halo sign was detected in 94% of first disease relapses with a lower mean

						number of segments with halo and sum of halo IMT compared to disease onset (2.9 ± 1.6 mm *vs.* 4.9 ± 1.5 mm, *P* = 0.0012; 2.0 ± 1.1 mm *vs.* 4.5 ± 2.0 mm, *P* = 0.0012)
Seitz *et al.*, 2021[23]	Prospective cohort	18	TA, AX, SC	Baseline, day 3, weeks 4, 8, 24 and 52	TA: L8-i18 MHz linear hockey stick AX/SC: ML6-15 MHz or 9L-D linear (LOGIQ-E9, GE) - 7 patients TA: 8.8-22 MHz hockey-stick AX/SC: 4-11 MHz vascular and 4-18 MHz matrix (Aplio i800, Canon) - 11 patients	After GC pulses for 3 days followed by TCZ monotherapy for 52 weeks 3/18 patients achieved remission within 31 days and 14/18 within 24 weeks TA IMT (16 patients): sharp decline on day 2/3, followed by an increase to baseline levels at week 4 and a subsequent slow decrease until week 52 AX/SC IMT (6 patients): sharp decline on day 2/3, followed by a slow increase up to week 8, a plateau until week 24, and a subtle decline until week 52; new signal of vasculitis in 3/6 patients at week 4
Dejaco *et al.*, 2022[38]	Prospective cohort	52	TA, AX	Baseline, weeks 1, 3, 6, 12 and 24	L8-i18 MHz linear hockey stick (LOGIQ-E9, GE) - Portugal and Linear 6-18 MHz (MyLab 7, Esaote) - Italy	OGUS showed significant and large to very large standardized mean differences between baseline and all time points (from -1.19 to -2.16) OGUS showed a significant correlation with ESR (0.48), CRP (0.43) and BVAS (0.37) The likelihood of achieving disease remission was lower in patients with higher OGUS values (OR 0.34; 95%CI: 0.18-0.63)
Nielsen *et al.*, 2023[24]	Prospective cohort	47	TA, AX, carotid	Baseline, 8 weeks, 24 weeks and 15 months	Linear 5-18 MHz (EUP-L75) (HI VISION Avius, Hitachi)	TA-based scores: showed significant and moderate to large standard response means between baseline and all time points (-1.49 to -0.66) LV-based scores: showed small to moderate standard response means between baseline and all time points (-0.48 to 0.01) and most often were not statistically significant OGUS showed a large magnitude of change and was considered the score least prone to potential bias OGUS and TA-based scores showed a significant, moderate correlation with CRP, and patient and physician global (0.27-0.45), and a weak correlation with hemoglobin and platelets (0.16-0.32)

AX: Axillary arteries; BVAS: birmingham vasculitis activity score; CRP: C-reactive protein; DMARDs: disease-modifying antirheumatic drugs; ESR: erythrocyte sedimentation rate; GE: general electric; GC: glucocorticoids; GCA: giant cell arteritis; IMT: intima-media thickness; LV: large vessels; N: number; NP: not provided; OGUS: OMERACT GCA ultrasonography score; OR: odds ratio; SC: subclavian arteries; TA: temporal arteries; TCZ: tocilizumab.

with GCA and in 4/4 patients with PMR, although all patients were in clinical remission when the second ultrasound was performed, i.e., showed no disease-related symptoms or abnormal inflammatory markers. However, the investigators used a linear probe that only allowed a B-mode frequency of 5-10 MHz, which has an inferior diagnostic accuracy compared to the current probes recommended by the European Alliance of Associations for Rheumatology (EULAR) (≥ 15 MHz for temporal arteries)[3]. In addition, no data after six months were collected; therefore, it is not known if those 14/22 patients with persistent TA halo experienced more relapses or disease complications during further follow-up.

De Miguel *et al.* prospectively assessed 30 patients with GCA, in whom an ultrasound of the TAs, using a 9-14 MHz probe for greyscale, was performed every two weeks for the first month after GC initiation and then every four weeks until halo disappearance[25]. A total of 38 GCA occurrences, including those registered at disease onset and disease relapse, were detected in the 30 patients assessed, with halo resolution observed in 36 cases (94.7%) during follow-up. After the initiation of GC treatment, the mean time to halo resolution was 8.58 ± 7.32 weeks for patients with a GCA relapse and 11.25 ± 7.05 weeks for those experiencing their first occurrence. Ultrasound results were compared with clinical and laboratory data. Patients with a TA halo sign at baseline and during disease relapse were reported to have a higher mean ESR and CRP than patients at the time of halo disappearance. In addition, patients with halo disappearance had normal or lower values of ESR and CRP, compared to patients with halo persistence. A higher number of TA branches with halo before the initiation of treatment was related to greater values of CRP and ESR and to a delayed resolution of the halo sign, but there was no significant difference between the number of branches with halo sign of patients at baseline compared to patients with disease relapse. This study has established an important association between ultrasound findings and laboratory response. Nevertheless, the halo sign behavior within the first two weeks of treatment initiation was not evaluated, although a substantial decrease in the diagnostic sensitivity of temporal artery ultrasound has already been described only after four days of GC treatment[33]. To the best of our knowledge, no study has yet evaluated how other cranial arteries, aside from the TA, behave during disease follow-up.

Extracranial arteries

Extracranial large vessel (LV) involvement, affecting the aorta and its main branches, is frequent in GCA and studies investigating its behavior during the clinical course of GCA have also been conducted[17-24,34,35]. Schmidt *et al.* performed follow-up ultrasound examinations of the proximal arm arteries (i.e., subclavian, AXs and/or proximal brachial arteries) in 40 patients with LV-GCA, with a mean interval between baseline and second ultrasound of 39 ± 22 months[34]. The halo sign disappeared completely in only 30% of cases, decreased in 53%, remained unchanged in 8%, increased in 5%, and progressed to occlusion with collateral flow in 5%. No ischemic arm complications were reported during follow-up, and GC requirements were similar to control patients with GCA without LV involvement.

Czihal *et al.* performed a cross-sectional analysis of 34 patients with LV-GCA after a mean follow-up of 22 ± 17 months[22]. The last ultrasound of the proximal arm arteries showed that the halo sign had completely disappeared in only 32.4% of patients, consistent with the findings of Schmidt *et al.*[34]. In addition, the IMT, reported in 17 patients, showed a decrease from a mean of 1.8 ± 0.7 mm to 1.3 ± 0.4 mm in the right AX artery, and from a mean of 1.7 ± 0.8 mm to 1.2 ± 0.4 mm in the left AX artery. None of the patients developed new ischemic symptoms of the upper limbs during follow-up.

Bosch *et al.* published the results of an observational study with a mixed retrospective and prospective design, in which 73 patients with longstanding GCA (GC treatment ≥ 1 year) and AX involvement of the disease at baseline were assessed with ultrasound at various time points[18]. The AX arteries' IMT was reported to decrease within the first 18 months of treatment by -0.5 mm (range -2.77 to 0.50). In addition, the median IMT after a median disease duration of 48 months (16-137) was still 0.90 mm (0.46-2.20). Nevertheless, assessment of the proximal arm arteries at fixed time points was not performed in all the three studies.

Although GCA can affect the aorta, no research has been published on the use of ultrasound for monitoring aortic involvement in this disease. This is not unexpected, as the technical limitations of ultrasound make it challenging to perform serial assessments of the aorta consistently. Other non-invasive imaging techniques,

such as CT and MR angiography, are generally more appropriate for evaluating aortic involvement in GCA throughout the disease course.

Cranial and extracranial arteries

The most recent studies have predominantly concentrated on evaluating both types of arterial involvement through ultrasound[17,19-21,23,24,35], aligning with the EULAR recommendations in which both TA and AX should be assessed for diagnostic purposes[3]. Aschwanden *et al*. performed an ultrasound at baseline and at six months on 9 patients with LV-GCA in 11 arterial regions: TA, carotid (common, internal and external), vertebral, subclavian (SC), AX, femoral (common, deep and superficial) and popliteal arteries[35]. The study showed that 76/84 (90.4%) of affected vascular segments showed persistence of the ultrasound abnormalities described as "marginally enhanced echogenicity of the vessel wall" at six months despite the absence of signs of systemic inflammation.

In another study, Aschwanden *et al*. assessed the same arterial regions by ultrasound in 42 patients with LV-GCA at baseline and at 6, 12 and 24 months[17]. Among patients with TA involvement, while only 11/26 (42.3%) cases showed complete bilateral normalization of vasculitic findings, 22/26 (84.6%) demonstrated a reduction in vessel wall thickening at some point during follow-up [16 (61.5%) patients at 6 months, 21 (80.8%) patients at 12 months, and 22 (84.6%) at 24 months]. No improvement in vessel wall thickening was observed in 4/26 (15.4%) patients, and 2/26 (7.7%) developed new vessel wall thickening during follow-up without corresponding clinical disease activity. In addition, no differences between baseline ESR and CRP, cumulative GC dose, use of disease-modifying antirheumatic drugs (DMARDs), and number of relapses were reported between patients with (11/26) or without (15/26) complete normalization of ultrasound findings during follow-up. In cases of LV involvement, 19/42 (45%) patients showed a reduction in wall thickening at any time during follow-up, corresponding to a regression in 71/284 of the total thickened segments at baseline. The authors did not provide details on other vessel wall characteristics, so it is possible the thickened walls became more hyperechoic, indicating chronic changes rather than an acute halo sign, which could explain the high persistence of vessel wall thickening. Only one patient showed complete normalization of all vasculitic findings on ultrasound, and in three patients, there was an increase in arterial wall thickness compatible with a previous disease relapse in two patients (in the prior one and two months, respectively). Patients who exhibited a decrease in wall thickening in at least one LV segment during follow-up had significantly lower median CRP and ESR at baseline compared to those with persistent findings; however, no differences were found between groups in terms of occurrence of disease relapses, GC-cumulative doses, and need for DMARDs.

Ford *et al* retrospectively analyzed patients with newly diagnosed or established GCA who underwent follow-up ultrasound of the TA, AX, and SC arteries as part of the routine care, i.e., not using fixed time points[15]. Patients were followed for a median time of 5.1 (IQR 2.6-7.9) months. Of the 36 patients who had active vasculitis on baseline ultrasound, 15/36 (41.7%) had no arteritis at follow-up, 12/36 (33.3%) had a hyperechoic wall thickening, and 9/36 (25.0%) still had active arteritis. Ultrasonographic findings in the TA were more likely to change from active arteritis to no arteritis, whereas those in the AX frequently remained stable or showed slower improvement over time.

Sebastian *et al*. evaluated 22 consecutive patients with GCA treated with tocilizumab in a prospective study[36]. Ultrasound of the TA and AXs was performed in 21/22 patients pre- and post-initiation of treatment. Baseline and follow-up results (within a range of 3-12 months) were compared. Among the 54 arterial segments displaying a halo sign at baseline, 38/54 (70.4%) showed a decrease in IMT following the initiation of tocilizumab. The study did not provide details regarding the timing of ultrasound for the 30%

of arterial segments that did not exhibit a decrease in IMT after tocilizumab initiation.

Ponte *et al.* performed a cross-sectional analysis of all patients with GCA from the TABUL cohort[37] who exhibited a halo sign on ultrasound conducted within 7 days of starting GCs[20]. A consistent reduction in the halo size in the TAs was observed over time, with patients showing a significantly smaller halo IMT after more days of GC exposure [maximum halo size per patient r = -0.30, $P = 0.001$ ($n = 112$ patients); and all halos r = -0.23, $P < 0.001$ ($n = 395$ halos)]. Contrary to the TAs, no correlation was found between halo size and number of days on GCs for the AXs within the first seven days of treatment [maximum halo size per patient: r = -0.064, $P = 0.721$ ($n = 33$ patients), and all halos r = -0.044, $P = 0.764$ ($n = 44$ halos)]. However, this could be explained by the low number of patients with LV involvement included in the analyses, and due to the fact that in larger arteries, the halo sign takes significantly longer to diminish and resolve compared to the TAs[34,17,22]. These findings, although limited by the cross-sectional design of the analyses, established the reasoning for conducting prospective monitoring studies assessing the long-term association between the presence and thickness of the halo sign and disease activity in GCA. Thus, Ponte *et al.* proceeded to conduct a prospective evaluation of 49 patients with a new onset of ultrasound-proven GCA[19]. The number of TA and AX segments with halo was recorded and the halo IMT of each segment measured. Sensitivity to change was calculated between time points where over 80% of patients were evaluated. During the study period, 354 visits were recorded, a mean of 7.2 ± 3.8 visits per patient. Halo sensitivity to change was calculated at weeks 1, 3, 6, 12, and 24, revealing a significant standardized mean difference between all time points and baseline for TA halo features (including the sum of segments with halo, and sum and maximum halo IMT). For AX arteries, a significant difference in the sum and maximum halo IMT was observed only after week 6. In addition, a significant correlation between all TA halo features and ESR and CRP ($P < 0.05$) was verified, aligning with the results of De Miguel *et al.*, as well as with Birmingham Vasculitis Activity Score (BVAS) and GC cumulative dose ($P < 0.05$)[25]. No significant correlations were found for the AX halo features. Patients with a greater number of TA segments showing halo (OR 0.39, $P < 0.05$) and higher TA halo IMT values (OR 0.34, $P < 0.05$) were less likely to achieve disease remission. In contrast, AX halo features showed no association with attaining clinical remission ($P > 0.05$). Despite the fact that only 11/49 (22.4%) patients in this cohort had AX involvement, these findings support those found in the previous cross-sectional study by the same research group[20], which found no change in the AX halo IMT during the first 7 days of high-dose GC treatment, unlike the TA halo IMT. It also validates the findings from prior studies, in which AX halos have been reported to persist for a longer time than TA halos, irrespective of clinical remission[17,18,22,34,35]. Moreover, halo sign was present in 94% of first disease relapses, but with fewer segments showing halo sign and with lower halo IMT compared to disease onset.

Monti *et al.* retrospectively evaluated the utility of ultrasound in the routine clinical care of patients with suspected or established GCA in a single University Hospital (Oxford, UK)[21]. Patients underwent ultrasound at the discretion of the treating physicians. Over a period of 23 months, 377 ultrasounds of the TA and AX arteries were performed: 210/377 (56%) for first referrals of patients with suspected GCA, 89/377 (24%) to complement the regular follow-up of patients with established GCA, and 78/377 (21%) for patients with suspected GCA relapse. Of the 210 patients assessed for suspected GCA, 54 (26%) had a positive ultrasound, and of the 78 patients assessed for a possible GCA relapse, 29 (37%) had a positive ultrasound. Patients with a new onset of GCA more frequently displayed four or more arterial segments with a halo sign than patients with a clinical relapse of the disease (39% *vs.* 7.7%, $P = 0.008$), supporting the results observed by Ponte *et al.* but contrasting with De Miguel *et al.*[19,25]. Moreover, Monti *et al.*[21] also recorded details on the halo size in 174/377 (46%) ultrasound examinations, which corresponded to the last 7 months of the study period[19]. The mean halo thickness of the AX arteries was higher in the new onset

group compared to the relapsing group (1.6 ± 0.4 *vs.* 1.4 ± 0.2 mm, $P = 0.02$), although no difference was found for the TAs (0.6 ± 0.2 *vs.* 0.6 ± 0.1 mm, $P > 0.05$). Despite also reporting a higher sum of halo IMT for patients at disease onset, in comparison to their first clinical relapse (4.49 ± 1.95 *vs.* 2.01 ± 1.13, $P = 0.001$), Ponte *et al.* found that this difference was only verified for patients with TA involvement ($P = 0.001$) and not for patients with AX involvement ($P = 1.000$)[19].

Seitz *et al.* aimed to prospectively characterize the effect of an ultra-short GC treatment (500 mg of i.v. methylprednisolone/day for three days) followed by i.v. tocilizumab monotherapy (8 mg/kg) on the IMT of the TA, AX, and SCs[23]. Despite the small number of patients included - 18 patients - a sharp decline was demonstrated in the IMT of the TA, AX, and SCs after 2/3 days of treatment, corresponding to the period receiving methylprednisolone. In the TAs, this was followed by an increase in the IMT to baseline levels at week 4, and a subsequent gradual decrease in IMT coinciding with the improvement of symptoms and the attainment of clinical remission. For the AX and SCs, a similar decline in IMT was observed on day 2/3, followed by a slow increase up to week 8, reaching a plateau until week 24, and a subtle decline thereafter until week 52. However, in only 6/18 patients, involvement of the extracranial large arteries was documented.

Recently, Nielsen *et al.* prospectively examined the sensitivity to change and discriminative abilities of vascular ultrasonography scores for disease monitoring in GCA[24]. The study encompassed 47 patients diagnosed with GCA, who underwent prospective follow-up assessments at both week 8 and week 24, including ultrasound of the TA, AX, and carotid arteries. Furthermore, within this cohort, a subset of 24 patients was followed for an extended period of 15 months. The results demonstrated that ultrasound outcomes improved during the follow-up period starting from week 8. However, it was noted that only scores involving the TAs consistently showed statistically significant improvement, while those based on large vessels did not. Additionally, patients experiencing a relapse were more likely to display a positive TA ultrasound and an increase in ultrasonographic scores compared to those in clinical remission. In contrast, there were no significant differences in outcomes related to large vessels between relapsing and remitting patients.

In an effort to optimize the use of ultrasound for monitoring patients with GCA, particularly in clinical trials and research, the OMERACT has very recently developed a provisional ultrasound score named OMERACT GCA Ultrasonography Score (OGUS). It is determined by summing the IMT measurements for each assessed segment of the TA and AX arteries, and dividing by the corresponding rounded IMT cut-off values of each segment (common superficial TA: 0.4 mm; parietal and frontal branches: 0.3 mm; AX: 1.0 mm). The resulting value is then divided by the total number of segments evaluated. This approach offers a more objective and standardized method for evaluating disease activity, thus serving as a valuable monitoring tool in clinical practice and research[38]. However, it is still imperative that this scoring system undergoes further validation in a patient-based reliability exercise, as well as in independent cohorts of patients with GCA[38].

FINAL CONSIDERATIONS

The evidence regarding the value of ultrasound for the assessment of patients with GCA during follow-up has been steadily growing. In our review, we found a wide range of reported rates for persistent vasculitic changes varying from 5.3% to 90.5%. These discrepancies are likely influenced by several factors, including the types of arteries evaluated, the timing of assessments, differing definitions of improvement or persistence, and variations in ultrasound equipment. For studies that provided technical details, the B-mode frequency of the probes used ranged from 5-22 MHz for temporal arteries and 4-18 MHz for axillary

arteries[13,15,17-21,23-25,35,36,38]. Nonetheless, the overall findings indicate that ultrasound is a valuable tool for detecting vessel wall changes throughout the disease course and in response to treatment, with these changes showing a good correlation with inflammatory markers.

Despite the important advances demonstrated in the various studies discussed, the recent EULAR recommendations only advise patients to undergo ultrasound for disease monitoring when there is suspicion of relapse or in case of treatment with drugs blocking the interleukin-6 pathway (e.g., tocilizumab), in which CRP and ESR are unreliable[3]. Ultrasound is not routinely recommended for patients in clinical and laboratory remission, as the clinical significance of persistent ultrasound abnormalities in relation to therapeutic decisions and future outcomes remains unclear. Over the course of the disease, it is frequently observed that the halo sign becomes more chronic and less hypoechoic compared to baseline, often being reported simply as 'wall thickening'[15,17]. However, differentiating between wall thickening that indicates a halo sign in active disease and wall thickening associated with scarring in inactive disease can pose a significant challenge, especially for less experienced sonographers. These unclear findings commonly seen during follow-up can potentially lead to an overreporting of ultrasound abnormalities, which in turn could lead to unwarranted overtreatment. Nevertheless, the interpretation of ultrasound results during a suspected relapse can still be facilitated by the comparison with previous examinations, including assessments conducted during periods of inactive disease. Therefore, in our group's perspective, we deem it beneficial to perform at least one ultrasound evaluation after achieving clinical remission, establishing a baseline 'remission ultrasound' for future reference in the event of a suspected relapse during follow-up.

As the knowledge progresses on the use of ultrasound for managing patients with GCA, it is crucial that future research [Table 2] also explores the potential added value of regular ultrasounds for monitoring disease activity compared to clinical and laboratory monitoring alone. As it has been consistently described, the presence of a halo sign in ultrasound, indicative of acute inflammation, can provide valuable insights into the activity of the disease. Its characteristics, including number of affected arterial segments and the halo size/IMT, have shown associations with laboratory markers and response to treatment [Figure 1], with a distinct pattern noted in cranial and extracranial arteries [Figure 2], underscoring the ultrasound potential as a valuable monitoring tool for GCA. Recent advancements, such as the development of the OMERACT OGUS Score, have introduced a more standardized and objective approach to ultrasound-based monitoring. Therefore, it is imperative to conduct further validation studies, which would be instrumental in establishing a more definitive role for ultrasound in disease monitoring, not only to aid clinical practice but also to be included in international recommendations.

CONCLUSION

In summary, while ultrasound has demonstrated significant potential in detecting vessel wall changes through disease course and correlating with inflammatory markers in GCA, its routine use remains limited due to the variability in findings and the risk of overreporting abnormalities. Establishing a "remission ultrasound baseline" may enhance the interpretation of future results, but the true value of regular ultrasound monitoring versus traditional clinical and laboratory methods remains to be fully validated. Ongoing research and standardized scoring systems like the OMERACT OGUS Score are essential for refining the role of ultrasound in disease management and guiding future recommendations.

Table 2. Future research agenda

· Compare the outcomes of adding regular ultrasound monitoring to the standard clinical and laboratory assessment of disease activity in GCA
· Further examine the relationship between halo sign characteristics and disease activity, laboratory markers, and treatment response
· Study the distinct patterns of vessel wall changes in cranial versus extracranial arteries to refine monitoring approaches
· Validation of the OMERACT OGUS Score in additional independent cohorts
· Inclusion of ultrasound-based scores, such as OGUS, in the monitoring of patients in clinical trials to improve the assessment of treatment response and disease progression.

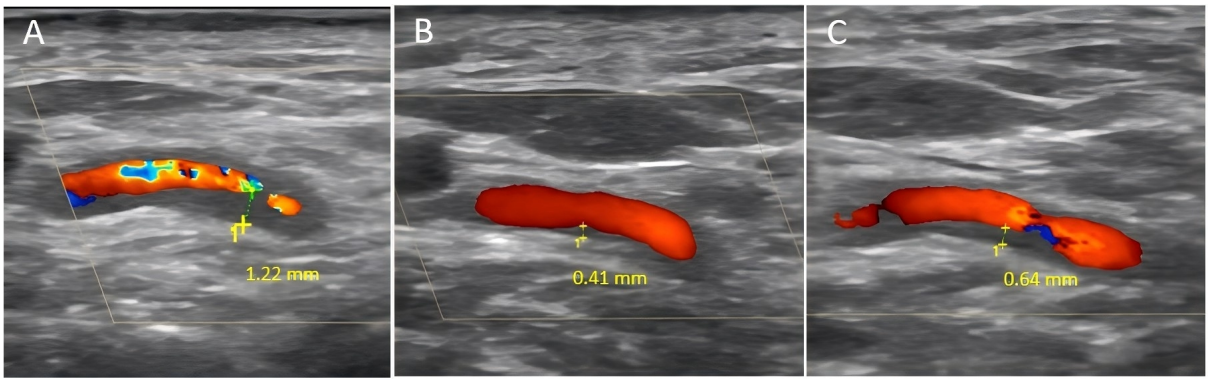

Figure 1. Temporal artery ultrasound of a patient with GCA at different disease stages. (A) At disease diagnosis with the LCSTA showing a significant halo sign (baseline); (B) At disease remission with no halo sign found in the LCSTA (6 months of follow-up); (C) At disease relapse with the LCSTA showing a halo sign (9 months of follow-up). IMT measurements are shown in yellow. GCA: Giant cell arteritis; IMT: intima-media thickness; LCSTA: left common superficial temporal artery.

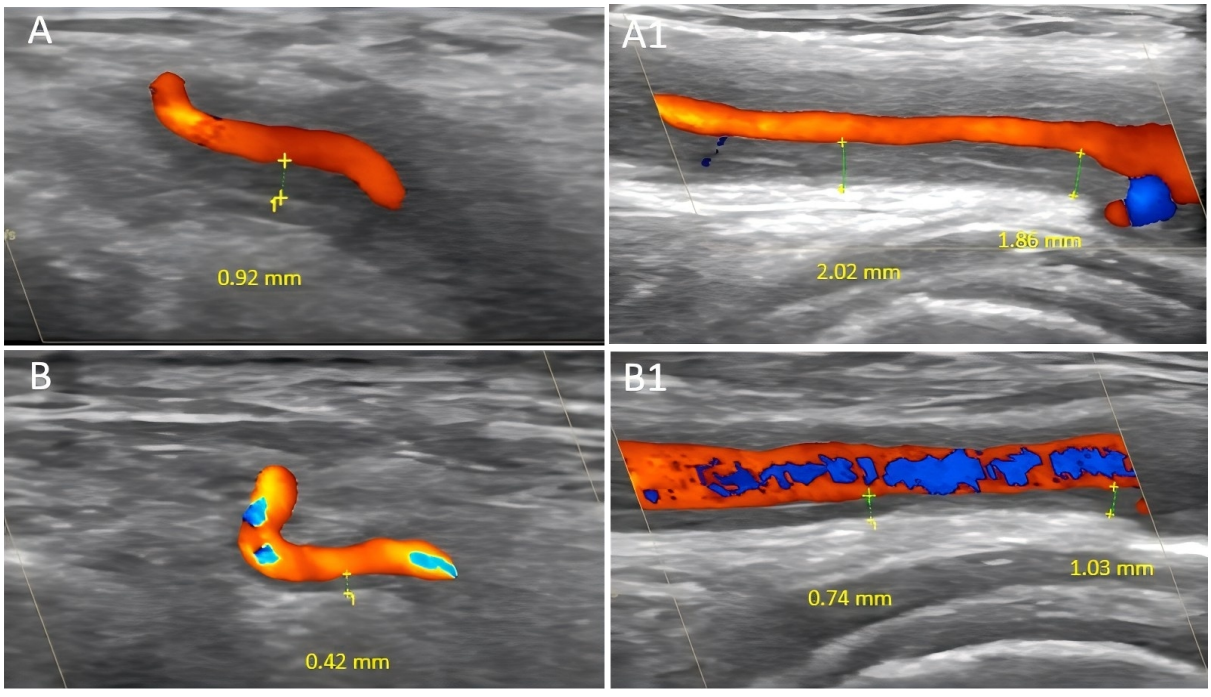

Figure 2. Ultrasound of the temporal and axillary arteries in a patient with GCA at baseline and 6 months. (A) At disease diagnosis with the LCSTA showing a significant halo sign (baseline); (A1) At disease diagnosis with the left axillary artery showing a significant halo sign (baseline); (B) At disease remission with no halo sign found in the LCSTA (6 months of follow-up); (B1) At disease remission with a halo sign still found in the left axillary artery (6 months of follow-up). IMT measurements are shown in yellow. GCA: Giant cell arteritis; IMT: intima-media thickness; LCSTA: left common superficial temporal artery.

DECLARATIONS

Authors' contributions

Conception, design, and writing: Martins-Martinho J
Writing: Sopa I
Conception, design, writing, and revision: Ponte C

Availability of data and materials

This review is based on previously published studies and data, which are available in the public domain. No new datasets were generated or analyzed during the current study.

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Ethical approval was not required for this study as it is a review of previously published literature.

Consent for publication

Not applicable since this is a review of previously published literature.

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