The utility and sensitivity of colour Doppler ultrasound in monitoring changes in giant cell arteritis

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ABSTRACT

Objectives. *To explore the sensitivity to change of colour Doppler ultrasound (CDUS) in giant cell arteritis (GCA).*

Material and methods. *This was a blind, prospective study composed of 30 consecutive patients diagnosed with GCA. In 25 of the cases this was their first episode of GCA, and 13 of the cases were relapses. All participants had presented with at least 1 branch involvement in the basal sonography, and steroid treatment had been initiated. A CDUS was performed every 2 weeks during the first month, and every 4 weeks thereafter, until halo disappearance was observed in the bilateral parietal and frontal branches of the temporal superficial artery.*

Results. *Thirty-eight episodes of GCA in 30 different patients (19 women and 11 men; mean age, 79.24±4.76 years; range 70–88) were followed. Dark halo disappearance occurred in 95% of cases. The mean time until halo disappearance was observed was around 11 weeks, with 50% of cases showing halo disappearance within the first 8 weeks. The relapse cases appeared to have less arterial wall affectation than the primary GCA cases, reduced erythrocyte sedimentation rate ESR and an earlier loss of the halo sign. Patients with a smaller number of affected branches required less time for halo disappearance.*

Conclusion. *CDUS shows a sensitivity to change in GCA. Halo disappearance is rare before two weeks, and it frequently persists during the first two months after initiating steroid therapy. Our data emphasise the advantages of using CDUS to monitor GCA activity.*

Introduction

Giant cell arteritis (GCA) is the most common form of systemic inflammatory vasculitis in adults (1-5). GCA affects large elastic arteries, including the aorta and major proximal branches (6). During the last decade, ultrasonography (US) has attracted considerable interest as a non-invasive diagnostic tool for patients with suspected GCA (7), and three meta-analyses have reported the high value and validity of US in diagnosing GCA (3, 8, 9). These studies have suggested that the presence of a halo sign (a dark area around the vessel lumen, likely due to arterial wall oedema) is highly specific to GCA, and this specificity is particularly high if the halo is bilateral (1). Other advantages of colour Doppler ultrasound (CDUS) include limited cost (10), a relatively short time required for the examination and the absence of radiation. CDUS, which combines imaging with flow-velocity determination, can assess both vessel anatomy and luminal status, and it may detect early vessel wall alterations. US transducers have an upper resolution limit of 0.1 mm, which is at least ten-fold higher than a MRI (11). This high resolution power allows ultrasound to not only visualise the halo sign for diagnostic purposes but it can also be used to monitor disease activity. To date, few papers have explored this possibility. There is scarce information on the length of time required for halo disappearance after the introduction of steroid treatment, and no data exist regarding the monitoring utility of US. The erythrocyte sedimentation rate (ESR) is generally used in the monitoring and tapering of glucocorticoid therapy in GCA. However, the ESR is an useful yet imperfect indicator of disease activity because there have been documented cases of positive GCA biopsies with normal ESR, and in some reports, ESR below 30 mm/hour have been documented in as many as 22.5% of cases at the time of diagnosis (12, 13). The C-reactive protein (CRP) is more resilient to extraneous factors compared to the ESR, and it is believed by some to be a more sensitive indicator of disease activity (7, 14). However,

both the ESR and CRP can also be altered by concomitant diseases; therefore, additional data and a method for determining an objective outcome of GCA progression is warranted.

The objective of this study was to explore the sensitivity to change of CDUS in the monitoring and assessment of halo thickness to determine its utility as a predictor of disease activity and therapeutic response.

Material and methods

This was a blind, prospective study, comprised of 30 consecutive patients diagnosed with GCA. GCA diagnosis was based on the American College of Rheumatology (ACR) criteria and confirmed by the clinician. Biopsies were conducted in 14 patients. Medical history data, a clinical examination, routine laboratory examinations and the ESR were collected at the time of inclusion to the study and on every follow-up visit.

The study protocol was approved by an ethics board, and all subjects provided informed consent. Clinical decisions were made independently by the head clinician.

Ultrasonography

A baseline CDUS of the temporal superficial artery was performed. In the baseline CDUS, participants presented involvement of at least one of the branches, and steroid treatment was subsequently initiated. After the baseline ultrasonography, CDUS was repeated for all patients every 2 weeks in the first month and every 4 weeks thereafter, until involvement disappearance in all four branches of the temporal artery. All examinations were performed by an expert sonographer with more than five years of experience in GCA US examinations; the sonographer was blind to the clinical data and laboratory results. Baseline and follow-up examinations were conducted with the same protocol, using Logiq 9 equipment (General Electric Medical Systems, Milwaukee, WI, USA) with a 9–14 MHz probe for grey scale and 5–7.5 MHz probe for Doppler imaging. For colour Doppler imaging, a frequency of 7.5 MHz, a colour gain of 38 and PRF of 1.4 Hz were used.

Standardised examinations were conducted on the superficial temporal artery, including the longitudinal and transversal views of the frontal and parietal branches on both sides, as completely as possible. An ultrasound diagnosis of arteritis was made if a dark concentric halo surrounding a residual colour flow signal appeared in at least 1 vessel segment of the superficial temporal artery or its branches. We defined a halo as a homogeneous dark wall surrounding a colour Doppler signal of at least 0.3 mm in the longitudinal view at the time of peak systolic blood flow.

For reliability purposes, two readers reviewed a mean of five videos per patient, taken from 64 cases (32 with GCA and 32 without). Stored videos were collected showing the bilateral exploration results of the parietal and frontal branches of the temporal superficial artery. One reader performed another blinded, intra-reader reliability exercise after one month.

Statistical analysis

For statistical comparisons, we used an ANOVA to determine differences between groups and the Student's *t*-test for independent samples. A kappa test for inter-reader of the two readers was applied. SPSS version 17.0 was used for all statistical analyses.

Results

Demographic data

We studied 38 occurrences of GCA in 30 patients (19 women and 11 men; mean age, 79.24±4.76 years; range 70–88). Twenty-five episodes were the patients' first instances of GCA, and 13 were relapses. The mean ESR at diagnosis was 66.46±25.76 mm/hour (range 19–113). Five patients relapsed years after ceasing steroid treatment, and 8 patients relapsed during steroid treatment tapering.

Ultrasound data

Halo disappearance occurred in 36 (94.7%) cases during follow-up, with a mean time of 10.36±7.15 weeks and a median of 8 weeks, ranging from 2 to 30 weeks. Two patients dropped out during follow-up. One patient died at 32 weeks, and another patient died at 40 weeks; both patients had halo persistence at the previous ultrasound visit. As shown in Figure 1, only 2 patients showed halo sign resolution at week 2, and at week 8, the dark halo had completely disappeared in 19/36 (52.6%) of patients.

The mean time until halo disappearance after the initiation of corticosteroid treatment was 8.58±7.32 weeks for relapsed patients and 11.25±7.05 weeks for patients presenting with their first occurrence of GCA ($p<0.05$). Relapsed patients had a mean of 2.46±1.13 branches presenting a halo and the initial diagnosis group had a mean of 3.16±1.11 branches; however, this difference was not statistically significant ($p=0.08$).

The mean ESR at baseline was 66.46±25.76 mm/hour (range 19–113), and the mean CRP at baseline was 47.22±56.75 mg/dl (range 3–163,5).The mean ESR at the time of halo disappearance was 20.35±14.69 mm/hour (range 4–59), and the mean CRP at the time of halo disappearance was 6.82±5.43 mg/dl (range 0.83–20.6). This difference was statistically significant ($p<0.001$). The mean ESR at baseline in relapsed patients was 48.75±16.29 mm/hour (range 19–80) and their mean CRP was 18.63±16.80. This result was statistically significant compared to patients without relapse, who showed a higher mean ESR, 75.17±25.86 ($p<0.01$) and a higher mean CRP 65.97±65.65 ($p<0.001$).

In the 36 follow-up examinations showing halo disappearance, 23 were in women, and 13 were in men, with a mean halo disappearance time of 8.83±5.70 and 13.08±8.78 weeks, respectively. However, this gender difference was not statistically significant ($p=0.09$).

Table I demonstrates that patients with halo disappearance had a normal or lower ESR than patients with halo persistence, and that the ESR was statistically different when comparing the number of arterial branches with halo presence. Table II demonstrates that the number of initial branches presenting a halo was related to the time required to achieve US GCA remission.

The halo sign was found in almost two branches in 34 cases, with a mean halo disappearance time of 12.57±7.21 com-

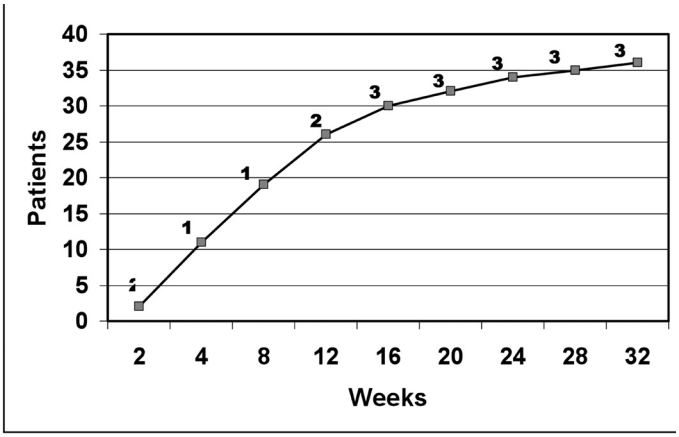

Fig. 1. Duration of dark halo disappearance.

pared with 6.46±5.28 weeks (p<0.01) in the 4 patients with only one branch involvement; 2 of these patients relapsed during the steroid tapering period.
A significant correlation was not found when comparing age or initial ESR value with halo disappearance time (p=0.39 and p=0.18, respectively).

Reliability
The kappa coefficient value between the 2 readers was 0.97 for the US GCA diagnosis; diagnosis discrepancies were found in only 3 cases. Considering all temporal branches observed (255), the 2 readers had a kappa value of 0.90; discrepancies existed for only 13 branches (5.1%), with both readers classifying 134 as negative for halo sign presence and 108 as positive for halo sign presence. The 13 discrepancies had a mean halo measurement of 0.26±0.116 mm, which is below the 0.3 mm threshold limit. The intra-observer kappa coefficient value was also excellent (0.96 in 255 branches), with discrepancies in only five branches and a mean measurement of 0.26±0.07 mm.

Discussion

The Outcome Measures in Rheumatology (OMERACT) filter has three component criteria: truth, discrimination and feasibility. Each component criterion must be addressed before a measure or test is accepted. Many recent publications have confirmed the truth field, *i.e.* the value of ultrasonography in diagnosing GCA (3, 8, 9). However, less evidence exists concerning the discrimination component in sensitivity to change. In the OMERACT, discrimination indicates whether a measure is able to discriminate situations that are of interest, involving states at a single time (for classification or progress) and states at different times (when measuring changes).

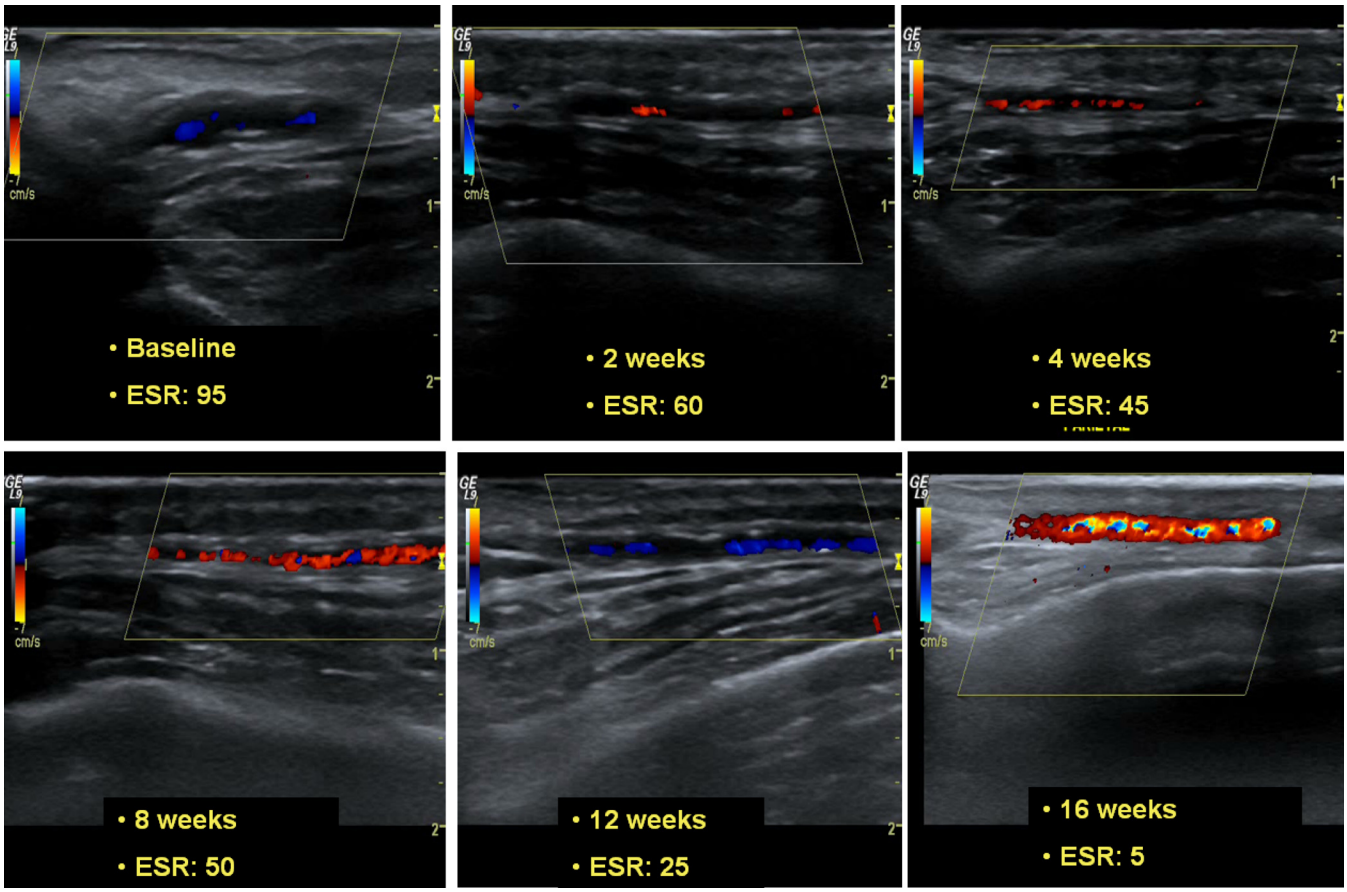

Fig. 2. Colour Doppler ultrasound follow-up (dark halo evolution in a patient between baseline and disappearance at week 16).

Table I. Number of affected temporal superficial branches and the mean ESR at follow-up.

Number of branches with halo	Mean ESR* ± SD (mm/hour)	Mean CRP** ± SD (mg/dl)
0	20.35 ± 14.69	6.82 ± 5.43
1	26.06 ± 23.98	20.70 ± 36.08
2	46.86 ± 31.18	17.93 ± 14.59
3	34.08 ± 31.45	30.36 ± 47.22
4	52.24 ± 34.95	40.51 ± 59.83

ESR: erythrocyte sedimentation rate; SD: standard deviation. *$p<0.001$; **$p<0.05$ between groups.

Table II. Number of affected basal temporal superficial branches and the duration (in weeks) until disappearance of halo.

Number of basal branches with halo (number of patients)	Number of weeks for halo disappearance* Mean ± SD
1 (4)	6.00 ± 2.31
2 (13)	7.23 ± 5.31
3 (1)	8.00
4 (18)	14.41 ± 7.44

*$p<0.05$ between groups.

In this paper, we were fundamentally interested in discrimination at different times to answer two questions. The first question concerned diagnostics (*e.g.* the time between steroid introduction and disappearance of halo). The second question involved exploring the ability of CDUS to monitor disease activity and treatment response (*e.g.* assessing halo persistence or disappearance in patients at different time points).

Since GCA is frequently a medical emergency, it is common for patients to arrive at our office with corticosteroid treatment with suspected GCA without sufficient diagnostic documentation. Previous evidence suggests that the biopsy profile is most representative in the first two weeks after steroid introduction (3, 15). However, the duration between steroid introduction and halo disappearance, allowing an US diagnosis, was unknown. Few studies have specifically evaluated this duration. Between 1997 and 2006, three studies addressed this issue. In the original study conducted by Schmidt *et al.* (16), the time of halo disappearance after initiating corticosteroid treatment was approximately 16 days (range 7–56). Karahalio *et al.* (1) observed halo disappearance after 22 days in 18 GCA patients, with 50% of patients showing halo disappearance at 2 weeks. Pfadenhauer *et al.* (17) found that only 5 patients showed abnormality reversal after 13 to 42 days. However, a more recent publication, in which halo disappearance time was the primary outcome, showed only 50% halo disappearance at 6 weeks and halo persistence at 6 months in 10/18 patients (18). The authors reported that patients with halo persistence were symptom-free and had normal laboratory parameters at the final CDUS assessment. Our data confirmed this slower halo resolution. A previous paper reported that patient symptoms improved with the halo disappearance, but Pérez *et al.* (18) and our results showed clinical improvement in patients before complete halo disappearance. In our study, we compared the presence of the halo with the ESR and CRP to explore construct validity. The results demonstrated that halo disappearance accompanied a significant reduction in ESR and CRP, which are two accepted measures of GCA activity in clinical practice. The discrepancy concerning our longer halo disappearance time may be due to our criterion for a positive halo sign (>0.3 mm), which is lower than the criteria used in the majority of other studies (>0.7 mm) (1). Only Schmidt reported a 0.3 mm measure in the sagittal view. In our study, we assessed the reliability of the halo measurement, and our results support 0.3 mm as a reliable lower measure in defining the halo sign. To the best of our knowledge, this has never been previously reported.

An additional advantage of CDUS in GCA diagnosis is relapse detection. Previous evidence and our data show that the halo sign disappeared with treatment for GCA. However, after halo disappearance, or years after treatment suspension, the halo sign occasionally reappeared with disease recurrence. This was especially important when relapse occurred during the steroid tapering period, in which the ESR could not have increased as the result of therapy. This is an advantage of CDUS because, when relapse is suspected from clinical symptoms, the ESR does not always increase. Therefore, CDUS can be also useful in examining ESR increases due to other causes or in examining GCA with normal or low ESR at the time of diagnosis, indicating that CDUS can be a fundamental tool in making clinical decisions.

Patients with relapse, especially during the tapering period of corticosteroid treatment, must increase steroid treatment, but this increase is usually only practiced in moderation. This is in agreement with our results demonstrating that in relapse, a lesser number of branches were affected, smaller ESR values were observed, and less time was required to achieve a negative halo sign, thereby reinforcing the validity of CDUS in monitoring this disease. Additionally, halo disappearance occurred more quickly in GCA patients experiencing their first flares, as these patients had a smaller number of affected temporal superficial branches than patients with more affected branches. This result has not been previously reported, and it requires future confirmation due to its important implications for future therapeutic decisions.

This study does have several limitations. A gold standard for validating the significance of halo disappearance time does not exist because repeated biopsies in patients with good responses to treatment is not feasible due to ethical reasons. Our observed times for halo resolution may be lower because we performed an exploration every 4 weeks after the first month. The disagreement between our higher halo disappearance time and other published data could also have resulted from differences in Doppler equipment. Older reports showed less time for halo disappearance. Differences in equipment sensitivity, colour persistence and Doppler enhancement settings could have

influence the results, indicating that Doppler equipment and qualification agencies require better standardisation. Another possible reason for our longer time to halo sign disappearance was the 0.3 mm halo size limit. However, this measure has also been used by previous authors, and it was supported by our results in patient follow-ups and by our qualitative assessments of reliability.

In summary, CDUS showed sensitivity to changes in GCA, with dark halo disappearance in 95% of cases. Halo disappearance was rare in the 2 weeks after initiating steroid therapy. The mean time of halo persistence was 11 weeks, with 50% of cases showing disappearance in the first 8 weeks. Relapse cases had less arterial wall involvement, smaller ESRs and a faster halo disappearance than initial GCA cases. Patients with a smaller number of affected branches required less time for halo disappearance. Using a criterion of 0.3 mm as the limit for identification of the halo sign appears to be reliable and shows construct validity. Our data emphasised the advantages of CDUS not only for GCA diagnosis but also in monitoring GCA activity.

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