Vascular Ultrasound for Giant Cell Arteritis: Establishing a Protocol Using Vascular Sonographers in a Fast-Track Clinic in the United States

Charles Oshinsky,1, 2 Alison M. Bays,1, 3 Ingeborg Sacksen,1 Elizabeth Jernberg,2 R. Eugene Zierler,1 Andreas P. Diamantopoulos,3, 4 Jean W. Liew,4, 5 Sarah H. Chung,1, 6 and P. Scott Pollock1

Objective. We developed a fast-track clinic (FTC) to expedite the evaluation of patients suspected of having giant cell arteritis (GCA) using vascular ultrasound. Though FTCs have demonstrated efficacy in Europe, no protociled clinic in the United States has been developed. This study introduces a new FTC model unique to the United States, using vascular sonographers, and describes the protocols used to develop reliable findings. We evaluate clinical outcomes using vascular ultrasound and temporal artery biopsy (TAB).

Methods. A retrospective review included all subjects referred to the University of Washington FTC aged 50 years old or older who received both ultrasound and TAB between November 2017 and November 2019. Ultrasound was performed by a vascular sonographer trained in GCA detection. Ultrasound results were read by a vascular surgeon and reviewed by four rheumatologists certified in musculoskeletal ultrasound who had completed a course in vascular ultrasound use in GCA and large-vessel vasculitis.

Results. A total of 43 subjects underwent both vascular ultrasound and TAB. Six subjects had both positive ultrasound and TAB results. There were also seven positive ultrasound results in patients with negative TAB results, most due to detection of large-vessel GCA (LV-GCA). All 29 subjects with negative ultrasound results had negative TAB results.

Conclusion. This is the first study in the United States to demonstrate a reliable FTC protocol using vascular sonographers. This protocol demonstrated good agreement between ultrasound and TAB and allowed for the detection of additional cases of LV-GCA by vascular ultrasound. Vascular ultrasound improved the rate of GCA diagnosis primarily by detecting additional cases of LV-GCA.

INTRODUCTION

Giant cell arteritis (GCA) is the most common primary vasculitis, and it may result in irreversible blindness if not treated promptly (1). Early diagnosis and treatment may protect against vision loss (2). Temporal artery biopsy (TAB) has been the gold standard for the diagnosis of GCA and is included in the 1990 American College of Rheumatology (ACR) GCA classification criteria (3). TAB is an invasive procedure with a wide range of reported sensitivities (39-95.1%) for the diagnosis of GCA (4,5). Imaging modalities such as 18F-fluorodeoxyglucose positron emission tomography (PET), magnetic resonance imaging, computed tomography (CT), and vascular ultrasound have all been explored in the diagnosis of GCA.

GCA was previously thought to be a disease affecting the cranial vasculature, with headaches being the predominant complaint. Imaging advances have expanded the concept of GCA...
beyond cranial large-vessel vasculitis to include extracranial arterial involvement, termed “large-vessel GCA” (LV-GCA) (1). Large-vessel involvement of GCA has been increasingly recognized over time, with incidence ranging from 20% to 80% on the basis of imaging modality and time of imaging relative to disease onset (6). Though TAB is insensitive for LV-GCA, vascular ultrasound is found to have a sensitivity of 73% to 77% and a specificity of 88% to 96% for LV-GCA as compared with PET/CT (7).

Many European countries use ultrasound to diagnose GCA (2,8,9). The European League Against Rheumatism (EULAR) published recommendations regarding the use of imaging in large-vessel vasculitis in 2018. These recommendations include the use of ultrasound as the preferred imaging modality (10). Ultrasound is noninvasive and more cost effective than TAB (5). According to EULAR recommendations, if a patient with a high suspicion of GCA has a positive ultrasound result, a TAB is not necessary to make the diagnosis. Inclusion of the axillary artery in ultrasound evaluation has improved the diagnostic accuracy of this test for GCA, particularly in cases of LV-GCA (11,12).

FTCs have evolved in European countries to quickly diagnose and treat GCA through use of ultrasound (6). FTCs in Europe typically include rheumatology evaluation and a vascular ultrasound performed by a rheumatologist in clinic. This reliance on ultrasound for cost-effective and accurate diagnosis allows clinicians to diagnose GCA without TAB while identifying large-vessel involvement in GCA. Two studies showed a reduced incidence of permanent sight loss in patients evaluated in the FTC as compared with the conventionally evaluated group (2,8).

In the United States, use of ultrasound to assist in diagnosis of GCA has increased in some centers (13). However, FTCs are in their infancy, and no reliable FTC protocol has been defined. Perhaps reflective of this lack of protocolized FTCs, intraoperator reliability of ultrasound may suffer. In European FTCs, ultrasound is performed by the rheumatologist, but given the realities of reimbursement and time constraints in the United States, such a model is not widely feasible in our system. Unlike EULAR recommendations, ultrasound is not yet endorsed by the ACR for diagnosis of GCA.

We developed a protocol for an FTC to evaluate patients for GCA by rapidly performing a rheumatology consultation, ultrasound of the cranial and large vessels, and TAB. This study is a retrospective review of this FTC. The aims of this study are to describe the protocol of the first FTC using vascular sonographers in the United States, evaluate the timeliness of evaluation and clinical outcomes in this FTC, and describe the concordance of vascular ultrasound and TAB.

**PATIENTS AND METHODS**

We formed an FTC in November 2017 at the University of Washington. Four rheumatologists provided on-call coverage for the FTC. Providers of any specialty who encountered a patient with suspected new-onset GCA paged the FTC team. If the referring provider was not a rheumatologist, patients were scheduled to see a rheumatologist within 48 hours. Vascular ultrasound was completed by a trained vascular sonographer within 24 hours, and a TAB was obtained within 7 days. If the patient had already been seen by a rheumatologist, they were directly scheduled for a vascular ultrasound and a TAB. Patients were referred to ophthalmology only if they had visual symptoms such as blurred vision, diplopia, or vision loss (Figure 1).

**Ultrasound evaluation.** A vascular sonographer performed all ultrasounds. The vascular sonographers who performed these ultrasounds were trained to detect GCA and large-vessel vasculitis during two separate training sessions 1 year apart. A rheumatologist (AD) with expertise in vascular ultrasound who had experience establishing European FTCs provided training. The ultrasound was performed using a Phillips EPIQ 7 ultrasound system with L12-3 (3-12 MHz) and L18-4 (22-2 MHz) transducers (Philips Healthcare). A detailed protocol for GCA evaluation by ultrasound was developed by the four rheumatologists (SP, IS, EJ, and AB), the vascular surgeon, and the trained sonographers. These rheumatologists were all certified in musculoskeletal ultrasound and attended a course in ultrasound evaluation of large-vessel vasculitides provided by European experts in vascular ultrasound who had established FTCs. The protocol was updated and revised during the 2 years of study. Completed ultrasound results were read by a vascular surgeon certified in vascular laboratory interpretation (Registered Physician in Vascular Interpretation certified).

All four rheumatologists reviewed every single ultrasound examination. Any discrepancy between the rheumatologists and the vascular surgeon was discussed in regular conferences by the four rheumatologists, the vascular ultrasonographer, and the vascular surgeon.

Blood vessels evaluated as part of the protocol include the temporal artery branches (common temporal, frontal, proximal, and distal and paniental) and the facial and occipital arteries (Figure 2). These blood vessels were evaluated for halo sign using compression. The large vessels evaluated included the common carotid arteries, internal carotid arteries, axillary arteries, and subclavian arteries. Intima-media thickness (IMT) was measured once in normal vessels and at the thickest areas of abnormal vessels. IMT cutoffs were based on published literature. An abnormal
IMT for the common carotid, internal carotid, and subclavian arteries was greater than 1.5 mm (14). An abnormal IMT for the axillary artery was greater than 1.0 mm (15). The ultrasound result was considered positive if there was a positive halo sign in the temporal arteries or if the IMT was greater than the established cutoff values of the large vessels and if changes characteristic for atherosclerotic arterial disease (irregular plaques with or without calcification) were absent. Flow velocities were recorded in areas of suspected arterial stenosis as well as in normal areas.

**TAB.** TAB was performed on all 43 subjects who received an ultrasound. TAB was performed unilaterally, with specimen length goal of at least 2 cm. The TAB was performed by ophthalmology, general surgery, or vascular surgery. The TAB was considered positive if any of the following was present: intimal proliferation with resulting luminal stenosis, disruption of the internal elastic lamina by a mononuclear cell infiltrate, invasion and necrosis of the media with an inflammatory infiltrate consisting predominantly of mononuclear cells, or giant cell

**Vascular Ultrasound Protocol**

| Halo sign                   | Right       | Left       |
|-----------------------------|-------------|------------|
| Common Temporal             | Yes/No      | Yes/No     |
| Frontal Temporal Proximal   | Yes/No      | Yes/No     |
| Frontal Temporal Distal     | Yes/No      | Yes/No     |
| Parietal                    | Yes/No      | Yes/No     |
| Facial                      | Yes/No      | Yes/No     |
| Occipital                   | Yes/No      | Yes/No     |

**Intimal Media Thickness**

| Common Carotid (cut-off 1.50 mm) | _ mm | _ mm |
|----------------------------------|------|------|
| Internal Carotid (cut-off 1.50 mm) | _ mm | _ mm |
| Subclavian (cut-off 1.50 mm)     | _ mm | _ mm |
| Axillary (cut-off 1.00 mm)       | _ mm | _ mm |

**Figure 1.** Fast-track clinic workflow. ED, emergency department; GCA, giant cell arteritis; PCP, primary care physician.

**Figure 2.** Each vessel was characterized as having a present or absent halo sign, and intimal media thickness measurements were obtained.
formation (16,17). Adventitial cell infiltration or vasculitis of the vasa vasorum was considered negative for GCA.

Chart review. A retrospective chart review of the FTC was performed and included patients from November 2017 through November 2019. All patients aged 50 years or more who received both an ultrasound and a TAB were included. Basic demographic and clinical data were collected for analysis. This was approved by the Institutional Review Board at the University of Washington. Study data were collected and managed using REDCap (Research Electronic Data Capture) tools hosted at the Institute of Translational Health Sciences (18).

Statistical analysis. We performed descriptive analyses and assessed differences between groups for categorical variables using Fisher’s exact test and differences between groups for continuous variables using the Mann-Whitney U test.

RESULTS

A total of 43 FTC patients received both a vascular ultrasound and a TAB (Table 1). The median age was 73 years old, and 70% were women. The median erythrocyte sedimentation rate and C-reactive protein were 47 mm/hour and 30 mg/L, respectively. The median number of days from referral to seeing rheumatology was 1 day, and the median from referral to ultrasound evaluation was 1 day. The median number of days on prednisone was 3 days prior to ultrasound and 7 days prior to TAB.

Of the 43 ultrasounds performed, 13 were positive, 29 were negative, and one was equivocal (with an abnormal temporal artery with a possible, poorly defined halo and diffuse wall thickening that did not meet defined cutoffs). Of the TABs, seven were positive, 36 were negative, and none were equivocal (Table 2). Six subjects had positive ultrasound and TAB results. There were no subjects with positive TAB results who also had a negative ultrasound, although one ultrasound in a subject with a positive TAB result was equivocal, notably after receiving high-dose intravenous glucocorticoids prior to the ultrasound. Importantly, there were no subjects with negative ultrasound results who had positive biopsy results.

Of the 13 subjects with positive ultrasound results, there were seven with negative TAB results (Table 2). The use of ultrasound in these seven subjects with negative TAB results identified important pathology. In five of seven subjects with positive ultrasound results and negative biopsy results, ultrasound identified only extracranial large-vessel vasculitis. One of seven subjects with positive ultrasound results and negative biopsy results had a temporal artery halo sign, and the last subject with positive ultrasound results and negative biopsy results had both a temporal artery halo sign and LV-GCA (Table 3).

### Table 1. Cohort characteristics and clinical outcomes

| Cohort characteristics | FTC (N = 43 Unless Otherwise Stated) |
|------------------------|-------------------------------------|
| **Cohort characteristics** |                                      |
| Age, median (IQR), yr  | 73 (68–79)                           |
| Female sex, n (%)      | 30 (70)                              |
| ESR, median (IQR), mm/h| 47 (29–72)                           |
| CRP, median (IQR), mg/L| 30 (10–73)                           |
| **Clinical outcomes**  |                                      |
| Time from FTC referral to ultrasound (n = 37), median (IQR), d | 1 (1–2) |
| Time from FTC activation to rheumatology evaluation (n = 27), median (IQR), d | 1 (1–2) |
| Time on prednisone prior to TAB (n =37), median (IQR), d | 7 (6–9) |
| Positive TAB results, n (%) | 7 (16) |
| Positive ultrasound results (%) | 13 (30) |
| Treated as GCA, n (%) | 20 (46.5) |
| Death, n (%) | 2 (5) |
| Permanent visual loss (n = 39), n (%) | 1 (2.5) |

Abbreviations: FTC, fast-track clinic; ESR, erythrocyte sedimentation rate; GCA, giant cell arteritis; IQR, interquartile range; TAB, temporal artery biopsy.

Fisher’s exact test was used for categorical variables, and the Mann-Whitney U test was used for continuous variables.

### Table 2. Concordance of ultrasound and TAB among the FTC cohort

| Positive TAB Results | Negative Ultrasound Results | Equivocal Ultrasound Results |
|----------------------|-----------------------------|-----------------------------|
| Positive TAB results | 6                           | 0                           | 1                           |
| Negative TAB results | 7                           | 29                          | 0                           |

Abbreviations: FTC, fast-track clinic; TAB, temporal artery biopsy.
Table 3. Specific ultrasound findings in the cohort with positive ultrasound results compared with TAB results

|                | Temporal Artery Halo Sign | Extracranial Large-Vessel Vasculitis | Cranial and Extracranial Large-Vessel Vasculitis |
|----------------|---------------------------|-------------------------------------|--------------------------------------------------|
| Positive TAB results | 2                         | 2                                   | 2                                                |
| Negative TAB results  | 1                         | 5                                   | 1                                                |

Abbreviation: TAB, temporal artery biopsy.

Twenty subjects (46.5% of evaluated subjects) were treated for GCA, including all subjects with positive biopsy and/or ultrasound results, as well as seven subjects with negative ultrasound results and negative TAB results, with clinically suspected diagnosis of GCA.

Two subjects evaluated by the FTC died. Both subjects were diagnosed with GCA. One of these subjects presented with blindness, the only subject in our cohort to experience permanent vision loss, which progressed after intravenous steroids. She was started on high-dose intravenous steroids and referred to the FTC. After 9 days, she died of cardiac arrest due to ventricular fibrillation. Another subject died of complications of infective endocarditis 4 months after being diagnosed with GCA.

DISCUSSION

This study demonstrates proof of concept of the first protocolized FTC for GCA diagnosis in the United States. Though FTCs have demonstrated efficacy in Europe, we made important modifications to the European model to make the FTC appropriate for the vastly different medical system in the United States, where ultrasound for GCA performed by the rheumatologist is often not feasible because of reimbursement and time constraints. Therefore, we created a protocol that emphasized specific training for vascular sonographers, with ultrasound interpretation by highly trained readers. We worked with a vascular surgeon, who interpreted the ultrasounds initially. Tedeschi et al recently described the experience of a multidisciplinary model at one center in the United States that uses ultrasound to facilitate GCA diagnosis. They defined a specific vascular ultrasound protocol, with ultrasound interpreted by vascular medicine physicians (13). Our study builds on this foundational understanding of the importance of ultrasound to diagnose GCA. Notably, we incorporate a multidisciplinary model centered around ultrasound to a specific FTC that explicitly expedites ultrasound and rheumatology evaluation to quickly diagnose and manage GCA.

In two prior European studies, FTCs demonstrated low rates of visual complications, demonstrating the efficacy of this treatment paradigm (2,8). Our FTC model also facilitated expedient TAB, the ACR-endorsed diagnostic modality. Notably, no subjects with positive TAB results had negative ultrasound results. Vascular ultrasound nearly doubled the rate of GCA diagnosis, primarily by detecting cases of LV-GCA. Ultrasound is less invasive than TAB, is more cost effective, and can often be obtained more quickly (5,6). The increased sensitivity for LV-GCA, cost effectiveness, and expedient ease of use in a protocolized center highlight the vital but often neglected role of ultrasound in the United States. Given the improved sensitivity of ultrasound for LV-GCA, we anticipate that, when appropriate, there will be a reduction in the need for TAB in the evaluation of GCA as has occurred in European centers that have developed FTCs.

Two subjects diagnosed with GCA died. This mortality does not indicate a failure of the FTC, as both subjects were treated and evaluated quickly and appropriately, but does underscore the need for FTCs that can quickly and accurately diagnose GCA to limit morbidity and mortality.

Ultrasound for GCA differs considerably from standard vascular sonography, and specialized training is necessary to obtain accurate results. For this reason, rheumatologists in our FTC received focused training in vascular ultrasounds for GCA, the vascular sonographers received focused training from an expert, we developed a detailed protocol for ultrasound evaluation of GCA, and we used high-frequency ultrasound probes.

As there are serious consequences to underdiagnosis or overdiagnosis of GCA due to inadequate training, protocols, or equipment; on the basis of our experiences, we recommend the following be built into any FTC using vascular sonographers: 1) training of vascular sonographers should be done by rheumatologists or other vasculitis experts knowledgeable in vascular ultrasound; 2) there should be ongoing review of techniques, protocols, equipment, and probe use; 3) a limited number of sonographers with training and experience should be used at each center; 4) FTCs should be located at referral centers with high volumes of patients with vasculitis to ensure adequate training and recognition; 5) all positive and questionable scans and randomly selected negative scans should be reviewed by the panel of rheumatologists, especially during the first year of the GCA FTC; and 6) all patients with negative ultrasound but high clinical likelihood of GCA should have the ultrasound examination re-evaluated. Ultimately, we hope these recommendations will lead to a task force that will evaluate the need for specific training and certification.

Strengths of our study included protocolized, specific training of vascular sonographers as well as over-reading of results of ultrasounds by rheumatologists trained in vasculitis-specific vascular ultrasounds. Our study has limitations. We had a small sample size, limiting our ability to make further inference from our data. Our patient population and referral system also differed from those reported in Europe; in most cases, patients were initiated on steroids prior to referral, possibly affecting the sensitivity of ultrasound (19).
In conclusion, FTCs for the diagnosis of GCA using vascular ultrasound remain novel in the United States. Our model incorporating vascular sonographers and a vascular surgeon with over-reads by rheumatologists trained in vasculitis-specific vascular ultrasound was shown to be effective in the diagnosis of GCA. Furthermore, this FTC resulted in higher detection rates of GCA because of detection of LV-GCA. Future studies are needed to corroborate these findings and to define the diagnostic role of ultrasound in GCA in the United States. As has already been adopted by EULAR, such findings may lead to increased use of ultrasound, a cost-effective, rapid, and patient-acceptable modality, in the diagnosis of GCA in the United States.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Bays had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Bays, Sacksen, Jenberg, Zierler, Diamantopoulos, Liew, Chung, Pollock.
Acquisition of data. Bays, Sacksen, Pollock.
Analysis and interpretation of data. Bays, Sacksen, Oshinsky, Liew, Pollock.

REFERENCES

1. Dejaco C, Brouwer E, Mason JC, Buttgereit F, Matteson EL, Dasgupta B. Giant cell arteritis and polymyalgia rheumatica: current challenges and opportunities. Nat Rev Rheumatol 2017;13:579–92.
2. 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 (Oxford) 2016;55:66–70.
3. Hunder GG. Classification/diagnostic criteria for GCA/PMR. Clin Exp Rheumatol 2000;18 Suppl 20:4–5.
4. 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 (Oxford) 2020;59:1011–20.
5. Lugmani 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.
6. Quinn KA, Grayson PC. The role of vascular imaging to advance clinical care and research in large-vessel vasculitis. Curr Treatm Opt Rheumatol 2019;5:20–35.
7. Duftner C, Dejaco C, Sepriano A, Falzon L, Schmidt WA, 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.
8. 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 Suppl 89:103–6.
9. 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: executive summary. Rheumatology (Oxford) 2020;59:487–94.
10. 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.
11. Gribbons KB, Ponte C, Carette S, Craven A, Cuthbertson D, Hoffman GS, et al. Patterns of arterial disease in takayasu arteritis and giant cell arteritis. Arthritis Care Res (Hoboken) 2020;72:1615–24.
12. Monti S, Ponte C, Pereira C, Manzoni F, Klersy C, Rumi F, et al. The impact of disease extent and severity detected by quantitative ultrasound analysis in the diagnosis and outcome of giant cell arteritis. Rheumatology (Oxford) 2020;59:2299–307.
13. Tedeschi SK, Sobiesczyszczk PS, Ford JA, Dilorio MA, Docken WP. Clinical experience with a multidisciplinary model of vascular ultrasound for the evaluation for giant cell arteritis. ACR Open Rheumatol 2021;3:147–153.
14. Schmidt WA, Seifert A, Gronnica-Ihle E, Krause A, Natusch A. Ultrasound of proximal upper extremity arteries to increase the diagnostic yield in large-vessel giant cell arteritis. Rheumatology (Oxford) 2008;47:96–101.
15. 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 (Oxford) 2017;56:1632.
16. 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.
17. Małeżewski JJ, Younge BR, Fritzlen JT, Hunder GG, Goronzay 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. Mod Pathol 2017;30:788–96.
18. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Infom 2009;42:377–81.
19. Ponte C, Serafim AS, Monti S, Fernandes E, Lee E, Singh S, et al. Early variation of ultrasound halo sign with treatment and relation with clinical features in patients with giant cell arteritis. Rheumatology (Oxford) 2020;59:3717–26.