Author’s response to reviews

Title: Halo Score (Temporal artery, its branches and Axillary artery) as a diagnostic, prognostic and disease monitoring tool for Giant Cell Arteritis (GCA)

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Author’s response to reviews:

Dear Editor,

Thank you for provisionally agreeing to accept and giving us the opportunity to submit the revised manuscript titled “Halo Score (Temporal artery, its branches and Axillary artery) as a diagnostic, prognostic and disease monitoring tool for Giant Cell Arteritis (GCA)”. We are grateful to the reviewers’ feedback and for their valuable comments on our paper.

We have responded to all the suggestions to the best of our ability. As you have suggested, we are submitting a clean copy of the revised manuscript without any changes highlighted. However, we have included a detailed response to each reviewer/editorial point raised, describing exactly what amendments have been made to the manuscript text and where these can be viewed. This revised submission has been made entirely according to editorial guidelines.
Here is a point-by-point response to the reviewers’ comments and concerns

Comments from Reviewer 1

Comment 1: Inherent methodological problems should be addressed (operator’s experience, limitations of colour duplex sonography in-wall morphology assessment of small arteries). Requirements for ultrasound imaging (high-frequency linear transducer &gt; 15 MHz) and operator’s experience should be predefined.

Response: We would like to thank you for your insightful comment. We agree with this comment, and these have been addressed as below:

Operator’s experience (included in page 11)
- All sonographers participating in this study have experience of scanning more than 30 people with temporal artery and axillary scans and at least 5 cases with GCA.
- All sonographers have completed either face to face or web-based training on the temporal artery and axillary artery scanning requirements for this study.
- All sonographers have completed the online BSR e-learning module on Ultrasound scanning for LVV
- We have documented the experience of sonographers and equipment characteristics with completion of a standardised form (attached- Appendix 4)

Limitations of colour duplex sonography in wall morphology assessment of small arteries
- Vascular colour duplex ultrasound is a fast-growing initial investigation in vast majority of vascular pathologies due to its cost effectiveness, non-invasiveness and repeatability as a clinic-based investigation. Also, it is useful to study the haemodynamic and morphology of the blood vessel. (Oglat et al. 2018).
- Each vessel has its own blood flow and waveform due to its vessel wall morphology. Thus, the interpretation of the results varies between the size of the vessels. Small arteries require careful interpretation of the results due to their relatively smaller vessel wall thickness compared to larger vessels. Therefore, HAS GCA study will validate a cut off values for this vessel wall thickness for these arteries.

OMERACT web-based and patient-based exercises study (Stavros et al. 2018) stressed the importance of validating the IMT in GCA. It also pointed out the potential limitations such as the model of the machine, the experience of the sonographer and other co-existing pathology of the vessels like atherosclerosis or occlusion.

EULAR recommends, an early imaging test in suspected GCA patients where the high expertise and prompt availability of the imaging technique. (Dejaco et al. 2018). Ultrasound should be the first imaging investigation in predominantly suspected in cranial GCA. It also noted the sensitivity and specificity of the test vary with the pre-test probability. In equivocal or negative US with high clinical probability, it suggests seeking alternative investigations such as TAB or PET CT.
Requirements for ultrasound imaging (high-frequency linear transducer ≥ 15 MHz) for HAS-GCA (these are also included in the HAS-GCA protocol)

We will follow EULAR recommendations for LVV imaging as below

- The B-mode frequency should be ≥15 MHz for temporal arteries and 7–15 MHz for extracranial supra-aortic arteries. Image depth should be 10–20 mm for temporal arteries and 30–40 mm for extracranial supra-aortic arteries.
- The focus should be at the level of the artery. The B-mode gain should be adjusted to avoid the anechoic appearance of the artery wall. The colour Doppler gain should be adjusted to avoid underfilling or overfilling of the vessel lumen.
- Colour Doppler mode is preferred over power Doppler mode. Tissue harmonic imaging may improve the delineation of the intima-media complex.
- Doppler frequencies of 7–12 MHz and 4–8 MHz should be applied for the temporal and for the extracranial supra-aortic arteries, respectively. PRF should be 2–3.5 kHz and 3–4 kHz, respectively. The angle between sound waves and artery should be ≤60°.

Comment 2: Different modes of wall thickness assessment of the temporal arteries should be discussed (IMT measurement in the longitudinal plane using colour duplex sonography vs. temporal artery compression sonography)?

Response: We thank you for this comment and please find our response below

- In this HAS-GCA study, for temporal and axillary ultrasound, we are following all the operational procedures for GCA diagnosis confirmation, image acquisition and measurement as required by several multi-centre international clinical trials in GCA (such as the Sanofi trial of Sarilumab in GCA – unfortunately currently paused because of COVID-19 pandemic)

- we use temporal artery compression to confirm all diagnoses of GCA. For every patient included in HAS GCA, it is a requirement to demonstrate ‘Compression sign’ positivity in the transverse plane with a video. A non-compressive halo is the key diagnostic lesion of GCA.

Comment 3: Introduction should be shortened, and Discussion should be more comprehensive, including current evidence regarding imaging (ultrasound) prediction of the clinical course of GCA (e.g., PMID 30544199, 25659455).

Response: Thank you for this comment.

- We have expanded the discussion section in the manuscript as suggested

Comments from Reviewer 2

Comment 1: on a single vessel level; reduction of on a 3-scale qualitative scoring system of the TA and the larger arteries had not shown in a retrospective analysis any correlation of reduction of the vessel wall and relapse or on cumulative steroid dose was seen (Aschwanden M, Schegk E, Imfeld S, Staub D, Rottenburger C, Berger CT, Daikeler T. Rheumatology (Oxford). 2019 May 1;58(5):792-797 Vessel wall plasticity in large vessel giant cell arteritis: an ultrasound follow-up study) so you might consider including more patients if the correlation is weaker
Response: Thank you for this comment. (included in the discussion section)

- In this study by Aschwanden M et al. showed there is a difference in reduction of the vessel wall thickness between the temporal artery and large vessel wall in response to the treatment by 85% and 45% respectively. A possible confounder was the inclusion of lower limb vessels including popliteal and carotid arteries which are prone to atherosclerosis. We are currently planning to recruit 272 patients in HAS GCA to include 68 diagnosed GCA, and we are focussing on arteries where non-GCA pathology is not frequent. However, we are open to increasing our sample size if required.

- Our case report “Excellent response to Leflunomide in a LV-GCA demonstrated simultaneously by clinical, laboratory, ultrasound and PET-CT parameters” (in press with JCR) showed a significant reduction in the axillary artery IMT in response to treatment.

- A case series published by Evans et al. 2016, showed the vessel wall reduction in large vessel GCA in response to Tocilizumab treatment. (Long-term efficacy and safety of tocilizumab in giant cell arteritis and large vessel vasculitis. Evans J, Steel L, Borg F, Dasgupta B. RMD Open. 2016 Jan 11;2(1):e000137. doi: 10.1136/rmdopen-2015-000137. eCollection 2016.)

- Our manuscript on “Efficacy and safety of Tocilizumab in GCA”, in 23 patients, is in preparation. US used to diagnose and monitor relapsing/refractory GCA shows significant changes in the temporal artery halo thickness (mean of 0.50 &amp; 0.17 mm pre and post TCZ) and axillary artery IMT (mean of 1.48 &amp; 0.98 mm pre &amp; post TCZ) over 12 months.

Comment 2: The score does not take into account the intensity of inflammation in one vessel segment (1 segment score 3 scores identical as three segments score 1 each) both scenarios are essentially not the same

Response: Thank you for this important comment. We have changed our data analysis section to reflect this.

- ‘In addition to the total halo score in the axillary and temporal artery, changes in individual vessel halo grades will be analysed’ has been included in the protocol.

Comment 3: How do you handle asymptomatic patients in remission with increasing Halo score during the FU examinations? this might be of importance especially under TCZ

Response: Thank you for this extremely important comment

- Changes to therapy will be made based on symptoms. However, in asymptomatic patients showing imaging abnormalities on the US, we will first carefully assess whether there are other signs and symptoms (which the patient may have overlooked) of active disease and we may follow up with additional investigations such as PETCT, CTA, MRA to look for activity and damage in other areas of the vascular tree. These patients will have more frequent follow up than as indicated in the study protocol.
We look forward to hearing from you in due course regarding our submission and to respond to any further questions and comments you may have.

Sincerely,

Prof Bhaskar Dasgupta
Corresponding author