PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	The challenges of diagnosis and management of giant cell arteritis in general practice: a multi-methods study
AUTHORS	Helliwell, Toby; Muller, Sara; Hider, Samantha; Prior, James A.; Richardson, Jane; Mallen, Christian

VERSION 1 – REVIEW

REVIEWER	Matthew Koster Mayo Clinic, Rochester, MN, USA
REVIEW RETURNED	14-Sep-2017

GENERAL COMMENTS	The manuscript entitled "Giant cell arteritis: challenges of diagnosis and management in general practice" by Helliwell and colleagues provides important insight into the difficulties of understanding and managing this condition among general practitioners in the U.K. Overall this is well written and provides helpful information to the medical community on this important topic. One major comment: Discussion: The authors note that the American College of Rheumatology criteria for GCA suggest that a positive biopsy is not essential for diagnosis of GCA. The criteria they refer to (Hunder et al. 1990) are "classification criteria". This is an inaccurate statement because there are no current diagnostic criteria for GCA. The ACR criteria were generated by looking at patient with vasculitis and trying to classify what type of vasculitis they had - NOT to diagnose individual patients or to determine if a patient had vasculitis vs not having vasculitis. While I agree that a positive temporal artery biopsy is not required to have a clinical diagnosis of GCA - using the ACR criteria to qualify diagnosis when they are classification criteria is a misrepresentation of what the criteria are intended for and perpetuates the common misunderstanding of how these criteria are to be use. Therefore this statement should be qualified or removed. A few minor comments: Introduction and Discussion Limitations on the timing of steroid initiation and temporal artery biopsy are mentioned in various areas of the article. It is also important to note that while ultrasound may be of benefit that the findings of inflammation on ultrasound can decrease within days of steroid initiation (Schmidt WA Ther Adv Musculoskeletal Dis 2014), whereas the findings of inflammation in temporal arteries in biopsy can be found in a high proportion of patients even several months out (Maleszewski JJ et al. Mod Pathology 2017).

	Materials/Methods: 2nd paragraph: refers to a PMR national cross sectional postal questionnaire survey. Was the survey for PMR or was it for GCA? If for PMR then this needs to be more fully explained. References: Reference 29 does not appear to be completely referenced - please confirm with the journal whether reference of website meets their standards

REVIEWER	Gianfranco Ferraccioli,MD,Professor Catholic University of the Sacred Heart, Italy
REVIEW RETURNED	01-Oct-2017

GENERAL COMMENTS	Interesting paper addressing an important issue, that is how are GCA patients managed in the early phase of their disease. Major comments. 1. The research agenda on how GCA was addressed by GPs did dot identify some key symptoms present in the early phase i.e. temporal artery tenderness , amaurosis, scalp tenderness, polymyalgia , claudication of the extremities as well as more atypical presentation i.e FUO, Cough, Anemia . Please specify why 2. The usefulness of Ultrasound of the temporal artery was never considered. Please specify why, since it is so simple and easy to be obtained 3. The delay in starting high dose steroids , in the case of suspect, was not quantitated ....please specify the percentage of GPs not starting

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Major comment:
“The authors note that the American College of Rheumatology criteria for GCA suggest that a positive biopsy is not essential for diagnosis of GCA. The criteria they refer to (Hunder et al. 1990) are "classification criteria". This is an inaccurate statement because there are no current diagnostic criteria for GCA. The ACR criteria were generated by looking at patient with vasculitis and trying to classify what type of vasculitis they had - NOT to diagnose individual patients or to determine if a patient had vasculitis vs not having vasculitis. While I agree that a positive temporal artery biopsy is not required to have a clinical diagnosis of GCA - using the ACR criteria to qualify diagnosis when they are classification criteria is a misrepresentation of what the criteria are intended for and perpetuates the common misunderstanding of how these criteria are to be use. Therefore this statement should be qualified or removed.”

Response: Thank you for pointing out this error. We completely agree with your statement regarding the misunderstanding of how these classification criteria are used and our experiences with PMR echo this issue with classification criteria often used as surrogates for diagnostic criteria in clinical practice.
We have therefore removed the sentence, as you suggested.

A few minor comments:
“Introduction and Discussion
Limitations on the timing of steroid initiation and temporal artery biopsy are mentioned in various areas of the article. It is also important to note that while ultrasound may be of benefit that the findings of inflammation on ultrasound can decrease within days of steroid initiation (Schmidt WA Ther Adv Musculoskeletal Dis 2014), whereas the findings of inflammation in temporal arteries in biopsy can be found in a high proportion of patients even several months out (Maleszewski JJ et al. Mod Pathology 2017).”

Response: Thank you for this important observation of what will be a critical factor in embedding Ultrasound into clinical pathways.
The following has been added to the relevant section in Background using the reference you supplied:
“although typical ultrasound features of GCA may diminish after just a few days of glucocorticoid treatment, whereas histological features of GCA may still be evident on TAB several months after initiation of treatment 6”

The following has been added to the relevant section in Recommendations again using the reference you supplied
“but will have to be rapidly available to clinicians given the importance of starting glucocorticoid treatment in GCA and the rapid effects treatment has on typical ultrasound features”

“Materials/Methods:
2nd paragraph: refers to a PMR national cross sectional postal questionnaire survey. Was the survey for PMR or was it for GCA? If for PMR then this needs to be more fully explained.”

Response: Thank you for highlighting this lack of clarity. We have amended the beginning of the section as below to add clarity to this issue.

“First, a national cross-sectional postal survey of 5000 randomly selected UK GPs was undertaken to investigate PMR and the closely associated illness of GCA, followed by a semi-structured telephone interview study with a purposive sample of survey responders to investigate in depth the challenges of diagnosis and management associated with PMR and GCA. The cross-sectional postal survey was undertaken first, with the findings used to help develop the topic guide for the interview study. This paper presents the combined findings from the two studies relating to GCA.”

“References:
Reference 29 does not appear to be completely referenced - please confirm with the journal whether reference of website meets their standards”

Response: Reference 29 has been altered to reflect the ICMJE standards outlined in section g part ii
“References should follow the standards summarized in the NLM's International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals. Sample References webpage was used to cite the website source address where the document is available

29) NHS Digital [Internet]. UK national information, data and IT systems for health and care services [cited 2017 Aug 25]. Available from: http://digital.nhs.uk/catalogue/PUB21772

Reviewer: 2
Major comments.
“1. The research agenda on how GCA was addressed by GPs did dot identify some key symptoms present in the early phase i.e. temporal artery tenderness , amaurosis, scalp tenderness, polymyalgia , claudication of the extremities as well as more atypical presentation i.e FUO, Cough, Anemia . Please specify why”

Response: Thankyou for this extremely important point with regards to the early and or atypical presentations of GCA. For the 2 questions we asked about relating to the symptoms and signs of giant cell arteritis, these were purposely asked as open, free text questions to reflect the combination and range of symptoms that GPs were using rather than giving just simple options to tick. However this meant that standard quantitative analysis was not possible and so a thematic content analysis was undertake. The results presented reflect the predominant themes. The absence of the key symptoms not presented as you point out including: amaurosis, claudication of the extremities as well as more atypical presentation i.e FUO, Cough, anaemia reflects the fact that GPs do not (or at least very few) use these more subtle features in routine practice.

Scalp tenderness was a theme that included temporal artery tenderness. We have added this for clarification within table 1.
We have altered the first paragraph of the conclusion to reinforce this point as follows and altered the first reference which remains relevant throughout the paper to reflect this change

"An increased focus on education and awareness of GCA (given its rarity and the range of presenting features including more subtle features such as limb claudication, constitutional symptoms, vascular bruits, asymmetry of pulses and or blood pressure, anaemia1) may aid better identification of potential GCA patients."

1) Dasgupta B, Giant Cell Arteritis Guideline Development Group. BSR and BHPR guidelines for the management of giant cell arteritis. Rheumatology 2010;49(8):1594–1597

“2. The usefulness of Ultrasound of the temporal artery was never considered. Please specify why, since it is so simple and easy to be obtained.”

Response: We agree that ultrasound is proving to be an extremely useful tool for the rapid diagnosis of GCA especially if it can be undertaken within a day or two of starting treatment with glucocorticoids. However, in the UK ultrasound scanning for GCA is still not widely available or accessible to GPs, being performed usually only at the discretion of hospital specialists. We think this may reflect why ultrasound scanning was not mentioned by participants - although we have no formal data to prove this.
We have modified the sentence in Discussion/recommendations as follows to reflect this:
“No participants discussed temporal artery ultrasound which can be used to help identify patients with GCA 5 and this may be because this imaging modality where available, is requested by the treating specialist and not by the GP.”

“3. The delay in starting high dose steroids , in the case of suspect, was not quantitated ....please specify the percentage of GPs not starting”

Response: Apologies, but we have to ask that the reviewer clarify this question please. We have presented, at the top of page 9 (and repeated below), the proportion of GPs who said they would not routinely initiate treatment prior to referral. We are unsure as to what additional data the reviewer would like us to present.

"…445 responders to the survey (35.6%) indicated that they would not routinely initiate treatment prior to referral…"

Once again, we thank the reviewers for their positive and encouraging comments. We hope we have addressed their concerns above and are freely available to discuss any further revisions or comments should there be any.

VERSION 2 – REVIEW

REVIEWER	Matthew Koster Mayo Clinic, Rochester, Minnesota, USA
REVIEW RETURNED	03-Nov-2017

GENERAL COMMENTS	Changes made are acceptable, no further comments/suggestions