January 23rd, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 16226-Review.doc).

Title: Giant Cell Arteritis: Current treatment and management

Author: Ponte C, Rodrigues AF, O'Neill L, Luqmani RA

Name of Journal: *World Journal of Clinical Cases*

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The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer
(1) No suggestions were made
(2) No suggestions were made
(3) All the corrections/ changes made are highlighted in yellow throughout the text

Minor comments:

1. In the abstract, the sentence "However, glucocorticoid therapy usually leads to significant toxicity in over 80% of the patients" would be better if you delete the word "usually".
→ Changed accordingly.

2. In the abstract, the sentence "Imaging techniques are important for screening aortic aneurysms and assessing patients with large-vessel involvement, but may also have an important role as disease biomarkers (e.g. ultrasound)" should be re-written as follows: "Imaging techniques (e.g. ultrasound) are clearly important screening tools for aortic aneurysms and assessing patients with large-vessel involvement, but may also have an important role as biomarkers of disease activity over time or in response to therapy".
→ Changed accordingly.

3. Under Bone Protection, does ACR refer to the American College of Rheumatology? If so, spell it out before the abbreviation.
→ Changed accordingly.

4. In order to avoid confusion, it might be useful to explain that there are imaging biomarkers and molecular biomarkers.
→ I re-wrote the management section according to your comment, separating it into three parts: "Molecular markers", "Imaging" and "Follow-up". I think it is more perceptible now.

Major comments:

1. Under Glucocorticoids you state that: [Glucocorticoids] "in most cases are able to provide complete symptomatic relief within 24-48 hours". Are the non-ocular exceptions also explained by the "latent period of up to 5 days between starting treatment and controlling the arteritic process"?
→In our opinion yes, if you have interest please read page 1213 of "Hayreh SS, Zimmerman B. Visual deterioration in giant cell arteritis patients while on high doses of corticosteroid therapy. Ophthalmology. 2003; 110:

1204–1215" for a better explanation. I extended the one I had in the text to make it easier to understand.

2. Explain why total duration of therapy is usually 2-3 years. Is it due to permanent remission, mortality from other causes in elderly patients or other reasons?
→ It is the average time taken for the patients to be safely weaned off steroids (no clinical features of active disease); I changed the sentence and added more data to make it more comprehensible.

3. Since glucocorticoids are the mainstay of therapy, it would be useful to add a table of what side effects might hamper GCA therapy.
→ I added a sentence in the introduction mentioning the major adverse events reported on long-term glucocorticoid use in GCA (from Proven *et al*). We thought it made more sense than putting all the known steroid side effects which are not specific for GCA in a table, I hope you agree.

4. It is important to mention (in the text or a table [see Dtsch Arztebl Int. May 2013; 110(21): 376–386]) the various eye manifestations in GCA. Note the importance of ocular problems by emphasizing that visual loss is usually permanent.
→Done, although this article is not focused on the disease manifestations of GCA, we wrote a bit in the text (introduction and induction-corticoids) and in a table adapted from Dtsch Arztebl *et al*.

5. If high dose aspirin is required to suppress IFNγ, why is low dose aspirin therapy recommended?
→ Because other effects of aspirin are beneficial. Normally, at sites of vascular injury thromboxane A2 is produced, enhancing platelets activation, thrombus deposition, vasoconstriction and release of PDGF. That is way is prudent to add low dose aspirin, especially when in combination with steroids (which can have some pro-coagulant effect by not being able to inhibit the generation of thromboxane A2 - according to Conn *et al* 1988 [reference in the text])
In addition, in clinical practice, because of its important side effects, it would be impossible to associate clinically relevant doses of aspirin (20-100 mg/kg) to prednisolone so we just give low doses. If you prefer we can just take the IFNγ story out.

6. Bley et al. (reference 83) suggested that high-resolution MR imaging is 97% specific for GCA. Nevertheless, MRI commonly misses mild inflammatory changes in vessels and is not useful for the evaluation of small-vessel disease. In the elderly, disease processes such as atherosclerosis are far more common than temporal arteritis and may result in similar MRI findings. A more detailed discussion of MRI specificity seems warranted.
→ Bley *et al* only analyzed 21 patients in their study; when they compared MRI with TAB (still the gold standard for the diagnosis in GCA) the MRI sensitivity was 100% and specificity 80% (not that great). The MRI specificity, when compared to the ACR criteria (which are not diagnostic criteria, but classification criteria that should not be used for diagnostic purposes), was 91.7% (probably the "97%" you might be referring [it might be missing the "1."]). The next reference, Rhéaume *et al* 2014, who have just presented their work at the ACR2014, analyzed through MRI 171 patients (much higher number). When MRI was compared to TAB the sensitivity was 93.6% and specificity 77.6% (again not that good) and they concluded that "the significance of a positive MRI is not well defined and this should be the focus of future research", meaning they don't really know very well how to overcome the issues of specificity in MRI. That is why we never mentioned the specificity (more studies are still warrant), but only the sensitivity, which meant to transmit that when the MRI of the cranium is negative the patient should not be thought as having GCA.
Regarding the arthrosclerosis leading to false positives, Bley *et al* mention exactly that problem (page 2476, 2nd paragraph) "Occlusions and stenoses of atherosclerotic origin may lead to a false-positive ultrasound diagnosis (7). With MRI, however, diagnosis is based on the intensity of

mural contrast enhancement, which is typically visualized as an inflammatory reaction and is not expected to occur in atherosclerotic changes of the vessel wall." Usually the most common false positives are seen due to the vascular remodeling that occurs during the disease recovery, which we have already mentioned in the text.
In addition, as you wrote, although MRI is not good to visualize small vessels, the temporal arteries (the most important arteries analyzed on their studies) are considered medium-vessel arteries.
Due to all the explanations above we didn't change the text.

7. Do surgical outcomes in GCA differ from those in patients with other etiologies of aortic disease?
→ Not known, now written in the text.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Clinical Cases*.

Sincerely yours,

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