Reviewer’s report

Title: One-year follow-up of patients with long-lasting post-herpetic neuralgia.

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Reviewer: Marius Birlea

Reviewer’s report:

The manuscript of Pica et al describes the follow up of postherpetic neuralgia in a group of 85 Italian Caucasian patients who presented to a Pain clinic 6 months or later after the onset of zoster rash. At enrollment and at 3, 6 and 12 months thereafter (T0, T3, T6, T12), pain and quality of life scores were obtained.

Major Compulsory Revisions:

The authors report significant improvement in the pain and quality of life scores for the majority of their patients, fact notable; it is likely that the improvement is related to the Pain clinic treatment although no details of that are given (i.e. onset and duration of treatment in the clinic, prior treatments addressing pain, selection of patients and possible randomization of treatment). The correlation of the pain scores, at various time points after inclusion in the study, with the antiviral treatment at the zoster onset (at least 6 months before T0) is probably interesting but at best speculative with the data presented here, as well as the discussion on gender differences. The current study, claimed to be prospective, makes correlations based on retrospective data, largely biased. VZV DNA was tested in blood of the majority of patients at T0, although with a method that appears relatively insensitive. Below are a few comments that address some specific points:

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Abstract:
The Conclusions can probably be better matched to the Results.

Background:
-I suggest that the background be shortened, with respect to the subject of the current study.

-Authors probably wanted to refer to Shingles vaccination (Zostavax) here: “…and the more recent introduction of vaccination against Varicella-zoster virus (VZV)”

Methods:
-May provide a better description of patients’ selection, mention if there was any randomization of treatment specific to the studied group, in order to minimize possible false correlations with the relative contribution of antiviral treatment at the time of zoster.
High cut-off (56 copies/ml): low sensitivity method.

Results:
- The vast majority of patients reported pre herpetic neuralgia (prodromal pain) of less than 1 day before rash. The authors may explain how relevant is for the current study, if the recall at 6 months is acceptable.
- The “intensity of rash” in Table 1 refers to the intensity of pain or extent of rash? The mix of the two terms is confusing (text and Table 1).
- Table 3: is it relevant without mentioning the pain treatment randomization?
- The average duration of pain, from rash onset, was 6 months in men (40% of the studied group), same as the date of study entry (T0) largely skewing the results.
- There was a clear trend of reduction in VAS at all time points, suggesting benefit from the pain treatment, not from antiviral therapy (Table 2). Can this be further clarified if initial antiviral treatment is addressed?
- May indicate the intensity of pain at the time of zoster (if measured or reported)
- The finding that less patients treated with antivirals at the time of zoster retain the neuropathic component of pain at T12 compared to patients who did not receive antivirals may be interesting (potentially suggesting less nerve damage); the authors may add a comment regarding the need of further confirmation on larger studies, prospective and randomized.

Discussion:
- The fact that “Viremia seems not to be associated with both intensity and duration of pain in our PHN patients”, is probably biased by low sensitivity method. A lengthy discussion about the VZV DNA findings here is probably unnecessary. The fact that VZV DNA is detected in the blood of PHN patients even at 80 months after zoster is remarkable and in line with other studies of blood or saliva in PHN.
- Agree with the authors that unifying method for VZV detection is advisable.
- The authors can add a comment why the use of antiviral therapy lead to lower VAS scores at T0 and T6 but not at T3 or T12?
- Almost immediate relief from the pain in men after inclusion in the study (average 6 months from rash onset = T0), compared to women, is difficult to explain and the authors’ discussion on gender differences and antiviral response has little support from the data presented.
- Agree with the authors that ideally, the treatment of postherpetic neuralgia should be tailored based on the possible mechanisms but it would have been better if the large discussion would have been supported by some details of the treatments utilized in the current study.

Miscellaneous:
- References 18 and 56 are identical.
-Figure 1 submitted twice.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.