Author’s response to reviews

Title: Hepatitis C-related cryoglobulinemic neuropathy: potential role of oxcarbazepine for pain control

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Hepatitis C-related cryoglobulinemic neuropathy: Potential role of oxcarbazepine for pain control.

Rita Moretti; Paola Caruso; Matteo Dal Ben; Silvia Gazzin and Claudio Tiribelli.

BMC Gastroenterology

Dear Editor,

We thanks the Editorial Office and the Reviewers for the positive consideration of our paper. To improve further the paper, we added the requested comments and citations, and carefully edited the manuscript.

All changes made in the Ms. are highlighted in different color (yellow). We think to have successfully dealt with the requests and improved the quality of the Ms. and look forward to its acceptance in BMC Gastroenterology.
We wish to remember that the Ms. was already submitted to BMC Gastroenterology and due to problem with the revision processes, the Editor Dr. Tovah Honor Aronin, agreed for a full fee waiver in case of publication.

Sincerely,

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Answer to the Reviewers
Questions in black, answers in red.

Giovanni Tarantino (Reviewer 1)
I would like congratulate authors on this interesting research. Minor but essential points:

Q1:
To give readers a broader view of the problem, involving therapy of extrahepatic manifestation of HCV infection, authors should emphasise that the classical antiviral therapy, when protracted, has ameliorated also complex features related the immune aspects associated with HCV infection, as evident in....Int J Mol Sci. 2015 Jun 19;16(6):14075-85. Successful and Safe Long-Term Standard Antiviral Therapy in a Patient with "Explosive" Immune Response in Course of HCV-Related Liver Cirrhosis.

A1:
We thanks the Reviewer for the suggestion. A comment has been added (lines 69-70).

“It is accepted nowadays that prolonged antiviral therapy led to a reduction of HCV-RNA levels, associated with a reduction of cryoglobulinemia [25].”

Q2:
Some precisations about the side-effects of oxcarbazepine, even though were not found, are advisable, such as ....mood disorders, suicide thoughts, low plasma sodium, etc. Authors should point out that treated patients gave their oral or written consent when possible.

A2:
A paragraph has been added (lines 187-194).

“Oxcarbazepine should be careful monitored by specialists, with reported side effects, which can be distinguished in: more common, but rapidly and spontaneously solving side effects (1:100): Blurred vision, disequilibrium, mental depression, emotional incontinence, cough and sore throat sensation. Less common (less than 1:1000): Agitation, awkwardness, mental confusion, persistent disequilibrium associated with orthostatic hypotension, fast or irregular heartbeat, thirst, muscle cramps, headache, skin rash, weakness. Usually they spontaneously disappeared, and they do not need a suppression of therapy. Rare (less than 1: 3500): Anxiety, burning feeling in the chest or stomach, hives or itching, irritability, restlessness, muscle pain or weakness, purple spots on the skin and rectal bleeding; these needs a careful medical examination, and the consequent decision to stop it.”

Theodoros Androutsakos (Reviewer 2)
Overall a good effort.
Q1:
However it needs to be revised as language is concerned (t.ex. it is not with sustained THE viral response, just sustained viral response).

A1:
We thanks the Reviever 2 for the accurate revision of the Ms. which improved the overall quality of the manuscript. We edited the text carefully.

Q2:
I think you need to show us some more data about the HCV status of the patients included in this study (viral load and genotype).

A2:
Details about the HCV status of the patients included in this study have been added to Table 2.

Patients (total 67) (number and %) FEATURES
Anti HCV antibodies 67/67 (100%)
Chronic Hepatitis 67/67 (100%)
Cirrhosis 6/67 (8.9%)
Presumed disease duration(years) 6.1 ± 2.7
Fibrosis score 1.9 ± 0.7
HAI score (Knodell RG et al. 1981) 6.5 ± 1.2
HCV genotype (number and %)
1 43 (64.1%)
2 1 (1.5%)
3 21 (31.3%)
4 2 (3%)

Q3:
Moreover you are saying that 44 patients interrupted their treatment due to adverse effects. I would like to know what kind of adverse effects were these.

A3:

We modify the sentence in order to clarify the patient therapy flow and side effects (lines 91-102).

“Neurological signs of peripheral neuropathic signs appeared for 11 patients 9.7 ± 2.1 months after the cessation of antiviral therapy even with a sustained viral response, and increase in the cryoglobulins serum level. 44 patients interrupted antiviral therapy (mean period of treatment of 7.6 9.7 ± 2.1) due to neurological symptoms such as anxiety and depression (18 patients), suicidal thoughts (6 patients), major sleeping disturbances, concentration difficulties and daily living executive complications (8 patients), apathy, chronic fatigue, loss of weight (12 patients). Drop out are in line with some data presented in Literature, i.e. by Manns et Al. [335, 34] All the 44 patients showed cryoglobulin neuropathic polyneuropathy 3.4 ±1.2 months after stopping antiviral therapy. 12 patients were strained to interrupt the IFN and ribavirin therapy (after mean time of therapy duration of 6.2 ± 3.9 months) due to the appearance of painful peripheral neuropathy, associated with an elevation of cryoglobulinemia, and therefore excluding the IFN-related neuropathy.

The new antiviral drugs (sofusbuvir, simeprevir, dalcatasvir, etc.) were not used, since at the time of the recruitment they were not available.”

Q4:

11 of your patients are said to have stopped treatment due to neuropathy, so they should not be included in this study since your patients have HCV related and not interferon related neuropathy.

A4:

The 11 patients were affected by cryoglobulin-neuropathy, induced by IFN therapy, and were included in the study. Cryoglobulinemia became evident when neuropatic pain and all the other signs of neuropathy apperared. However, a comment about the possible side effects of IFN alpha therapy have been added (lines 72-76, 175-177).

“On the other hand, the side effects of IFN alpha therapy are known, with the exacerbation of the symptoms of mixed cryoglobulinemia, with an exacerbation of the neuropathy, whit severe
myalgia, arthralgia [26, 27]. Moreover, there are different cases of described side effects of IFN alpha, such as demyelinating sensory neuropathy, neuropsychiatric symptoms, a possible bone marrow dyscrasia, a transient or definite worsening of hepatitis [22,28,29]”

“The role of interferon to exacerbate cryoglobulinemia related neuropathy is still under evaluation, although recent data obtained in 24 patients showed that interferon-free regimen with new drugs as sofosbuvir resulted in an almost complete clinical response of the vasculitis but still undefined effect on pain relief [43]”

Q5:

Last but not least looks like 50% of your patients have also HBV infection, unless what you mean is they had previous HBV infection, so I would like you to comment on that as well.

A5:

Details about the mentioned subjects have been added to Table 1.

<table>
<thead>
<tr>
<th>Patients (total 67)</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>50.4 ± 2.7</td>
</tr>
<tr>
<td>Sex ratio (M/F)</td>
<td>31/36</td>
</tr>
<tr>
<td>Apparent duration of disease (years)</td>
<td>4.1 ± 1.3</td>
</tr>
<tr>
<td>Albumin level (g/L)</td>
<td>39.7 ± 8.5</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>131.4 ± 16.7</td>
</tr>
<tr>
<td>Prothrombin time (%)</td>
<td>84.1 ± 12.2</td>
</tr>
<tr>
<td>Rheumatoid factors (n of pts and %)</td>
<td>41/67 (61%)</td>
</tr>
<tr>
<td>Mean Cryoglobulinemia(g/L)</td>
<td>0.27 ± 0.8</td>
</tr>
<tr>
<td>Cryoglobulinemia type</td>
<td></td>
</tr>
<tr>
<td>CGS TYPE II (n of pts and %)</td>
<td>42/67 (64%)</td>
</tr>
<tr>
<td>CGS TYPE III (n of pts and %)</td>
<td>25/67 (36%)</td>
</tr>
<tr>
<td>ANTI HCV Antibodies (n of pts and %)</td>
<td>67/67 (100%)</td>
</tr>
<tr>
<td>Test</td>
<td>No. of Pts</td>
</tr>
<tr>
<td>--------------------</td>
<td>------------</td>
</tr>
<tr>
<td>ANTI HBV Antibodies</td>
<td>35/67</td>
</tr>
<tr>
<td>Anti HBC</td>
<td>30</td>
</tr>
<tr>
<td>HBsAg</td>
<td>5</td>
</tr>
<tr>
<td>Anti HBS</td>
<td>30</td>
</tr>
<tr>
<td>HBeAG</td>
<td>0</td>
</tr>
<tr>
<td>AntiHBe</td>
<td>0</td>
</tr>
<tr>
<td>HCV RNA sequences in sera</td>
<td>49/67</td>
</tr>
</tbody>
</table>