

February 20, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 6515-review.doc).

Title: Cytokinome profile evaluation in patients with hepatitis C virus infection.
A review of the literature

Author: Francesca Capone, Eliana Guerriero, Giovanni Colonna, Patrizia Maio, Alessandra Mangia ,
Giuseppe Castello, Susan Costantini

Name of Journal: *World Journal of Gastroenterology*

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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

In details,

Reviewer (1)

This paper seems informative but has some concerns to be addressed. First, some abbreviations are difficult to understand. For example, LC in Table 1, 2, and 3 means cirrhosis with HCV infection? In Table 2, LCD means cirrhosis with HCV infection and type 2 diabetes?

We have inserted the meaning of the abbreviations evidencing that LC means patients with HCV-related cirrhosis, LCD means patients with HCV-related and type 2 diabetes.

Second, Figure 2 is completely the same as Figure 1 in Ref. 27. The source of Figure 2 should be indicated in the text or in figure legends.

We have prepared a new figure modifying the figure already present in ref. 27. However in the legend of figure 2 we have added that the data reported are the same showed in ref. 27

Reviewer (2)

However, there are several important questions to the authors:

1. It is not clear whether LC, LCD and HCC are HCV outcomes. If not, there is no sense to compare any "omics" of HCV patients with chronic hepatitis, LC, LCD and HCC and patients of other etiological groups.

All the patients present HCV with viral load. In fact in this review we report recent data obtained on patients with only HCV, with HCV-related cirrhosis, with HCV and type 2 diabetes, with HCV-related cirrhosis and type 2 diabetes and with HCV-related cirrhosis and hepatocellular carcinoma. Our aim was to identify what cytokines were index of only HCV infection presence and what cytokines modified their levels in copresence of cirrhosi and/or type diabetes and/or hepatocellular carcinoma. This is the reason also of the title of our review: Cytokinome profile evaluation in patients with hepatitis C virus infection

2. If you consider some cytokines to be important for differential diagnostics between different stages of liver injury, then use appropriate statistical approaches to show which levels of these cytokines have diagnostic meaning and which patients belong to the risk groups.

Although our results clearly indicate the use of some patterns of cytokines as a prognostic and

diagnostic tools, we are cautious about giving details that can be given only if you have a database with thousands of instances.

Thus, before to suggest the possibility to use specific cytokines in clinical diagnosis for different stages of liver injury, it is necessary to collect a greater number of patients and to repeat the evaluation of cytokinome profile. However correlating the cytokines resulted statistically different in some patients groups with clinical/biochemical data by Pearson correlation we can underline that:

i) HGF resulted to be up-regulated in the patients with HCV-related cirrhosis (LC) and not in those with only HCV, showed a negative correlation coefficient with albumin values, that are lower in LC patients, and, hence, can be index of the progression that from HCV leads to LC and HCC

ii) glucagon resulted higher in LCD patients than in those with LC, showed a significant positive correlation with glycaemia and body mass index (BMI) values and a negative correlation with albumin values, and, hence, can be used as index of co-presence of type 2 diabetes and cirrhosis in HCV patients

iii) sIL-6Ra was higher in LC patients than in those with HCC, showed a significant correlation with Child-Pugh score in LC patients, and, hence, can be index of progression from LC to HCC.

On the basis of these data, further studies will regard the validation of these data on a greater number of patients.

3. There is no great sense in showing the difference in cytokine levels between control and groups of patients, especially if you use multi-etiological groups.

Since that this manuscript is a review, we are reporting the data reported in our previous published papers. In particular, our aim is to indicate: i) the cytokines that are statistically different between the different patients groups compared to healthy controls and ii) the cytokines that are statistically different between the different patients groups. In fact we would like to evidence both what molecules can be index of liver diseases and what molecules can be index of liver disease progression and useful to obtain prognostic information.

4. In Fig2, there significant differences between parameters in various groups are not indicated

Moreover we have indicated with * the cytokines resulted statistically different between HCV and HCV-related LC patients.

5. It is pretty much clear now, that the functional role of cytokines depends those signal transduction pathways which they are able to activate and those liver cells that have receptors to these cytokines and thereby can transduce the signals. This point should be elaborated rather than demonstration of Fig.3 , which is in a way it is presented, makes no sense.

We have added the analysis of metabolic pathways in which the significant cytokines resulted to be involved, Table 4 and three new references.

Reviewer (3)

ACCEPT without revisions

Reviewer (4)

This manuscript is acceptable with some minor mistakes. Information of the numbers of the patients should be given for each study that was given in this paper, which is critical in such studies.

We inserted in the text the number of patients collected in each study.

In section 6 entitled "Cytokines evaluation in LC patients in presence and/or absence of HCC" a reference should be indicated after the first sentence, in which the results of a study were given.

These data have not been already published but they are reported in the paper that we have submitted to journal for publication.

In this document there is neither a running title nor key words. In addition pages were not numbered.

We inserted running title, keywords and page numbers

3 References and typesetting were corrected

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

Sincerely yours,

A handwritten signature in black ink, appearing to be 'P. Lakatos'.

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