May 19, 2016
Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 25927-Revised manusript.doc).

Title: Hepatitis C virus-associated B-cell non-Hodgkin's lymphomas
Author: Romeo-Gabriel Mihăilă

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 25927

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. I changed the article title. It is currently: Hepatitis C virus-associated B-cell non-Hodgkin's lymphomas.
2. I shortened the abstract:
The hepatitis C virus (HCV) infected patients are prone to develop bone marrow or various tissue infiltrates with monoclonal B cells, monoclonal B lymphocytosis or different types of B cell non Hodgkin's lymphoma (BCNHL), of which the most common are those with splenic marginal zone BCNHL, diffuse large BCNHL and follicular lymphoma. The association between chronic HCV infection and non Hodgkin's lymphoma has been observed especially in areas with high prevalence of this viral infection. Outside the limitations of some studies that have been conducted, there are also geographic, environmental, and genetic factors that contribute to the epidemiological differences. Various microenvironmental signals, such as cytokines, viral antigenic external stimulation of lymphocyte receptors by HCV antigens, and intercellular interactions contribute to B cell proliferation. HCV lymphotropism and chronic antigenic stimulation are involved in B-lymphocyte expansion, as mixted cryoglobulinemia or monoclonal gammopathy of undetermined significance, which can progress to BCNHL.HCV replication in B lymphocytes has oncogenic effect mediated by intracellular HCV proteins. It is also involved in an important induction of reactive oxygen species that can lead to permanent B lymphocyte damage, as DNA mutations, after binding to surface B-cell receptors. Post-transplant lymphoproliferative disorder could appear and it has a multiclonal potentiality that may develop into different types of lymphomas. The hematopoietic stem cell transplant made for lymphoma in HCV-infected patients can increase the risk of earlier progression to liver fibrosis and cirrhosis. HCV infected patients with indolent BCNHL who receive antiviral therapy can be potentially cured. Viral clearance was related to lymphoma response, fact that highlights the probable involvement of HCV in lymphomagenesis. Direct acting antiviral drugs could be a solution for the patients who did not tolerate or respond to interferon, as they seem to be safe and highly effective. The use of chemotherapy in combination with rituximab for the treatment of BCNHL in patients infected with HCV can produce liver dysfunction. The addition of immunotherapy with rituximab can increase the viral replication, and severe complications can occure especially in patients co-infected with HBV or immune immunodeficiency virus, in those with hepatocarcinoma, cirrhosis, or liver cytolysis. But the final result of standard immunochemotherapy applied to diffuse large BCNHL patients with HCV infection is not notably worse than in those without this viral infection. The treatment of patients chronically infected with HCV and having BCNHL is complex and requires a multidisciplinary approach and the risk / benefit ratio of rituximab treatment must be evaluated especially in those with

liver cytolysis.

3. I have added a table and a figure at the end of manuscript:

Table 1: The main therapeutical findings

Study findings	Reference
Antiviral treatment should be indicated in order to prevent lymphoma occurrence.	[2]
Low-grade malignant lymphomas can respond to antiviral therapy.	[26,51]
Non-Hodgkin's lymphoma with high grade of malignancy need immuno-chemotherapy associated treatment.	[7,15]
Antiviral treatment contributed to an improved outcome of HCV-infected patients with non-Hodgkin's lymphoma.	[16]
Antiviral treatment could be an alternative to chemo-immunotherapy in some cases.	[23]
Splenic marginal zone lymphoma is most frequently associated with HCV infection and can evolve favorably after HCV eradication.	[53]
HCV-infected patients with indolent BCNHL who receive antiviral therapy can be potentially cured.	[13]
Forty-four of HCV-infected patients with indolent BCNHL obtained a complete remission and 33% a partial response of lymphoma after antiviral therapy used as first-line treatment.	[55]
Viral clearance was related to lymphoma response.	[55]
The clinical response of lymphoma is dependent on HCV-RNA eradication.	[14]
The combined treatment with peginterferon and ribavirin proved to be useful for the treatment of BCNHL.	[56]
Repeated plasmapheresis are needed, if hyperviscosity is present, followed by antiviral +/- cytostatic therapy.	[24]
The administration of direct antiviral agents is useful in onset of therapy of patients with marginal zone BCNHL who have no severe complications, and early in those with diffuse large BCNHL in order to prevent the potential liver damage induced by the use of immunochemotherapy and avoid BCNHL relapse.	[56]
A chronic HCV-infected patient with splenic marginal zone lymphoma obtained rapid viral clearance and his lymphoma was cured with an interferon-free regimen based on NS3-NS4A inhibitor.	[57]
A HCV-infected female patient with chronic lymphocytic leukaemia received telaprevir-based triple therapy followed by successful result, without chronic lymphocytic leukaemia progression.	[58]
HCV-infected diffuse large BCNHL patients had a higher liver toxicity induced by immunochemotherapy and a higher delay of their chemotherapy application.	[59]
Severe liver toxicity (grade 3-4) was significantly more frequently found in diffuse large BCNHL patients infected with HCV treated also by immunotherapy compared with those treated only by chemotherapy.	[60]
The liver toxicity of grade 3-4 was significantly more frequently found in HCV-infected patients with diffuse large BCNHL treated with chemo-immunotherapy and the progression-free survival and overall survival were significantly shorter in comparison with those who received only chemotherapy.	[61]
Fourteen percent of HCV-infected patients with diffuse large BCNHL who received an anthracycline-based chemotherapy (with rituximab in 255 of them) developed severe liver toxicity.	[50]
A patient with diffuse large BCNHL and HCV infection developed a cholestatic hepatitis C after chemoimmunotherapy.	[62]
The addition of immunotherapy with rituximab can increase the viral replication.	[13]
The final result of standard immunochemotherapy applied to diffuse large BCNHL patients with HCV infection is not less good compared to those without this infection.	[13]

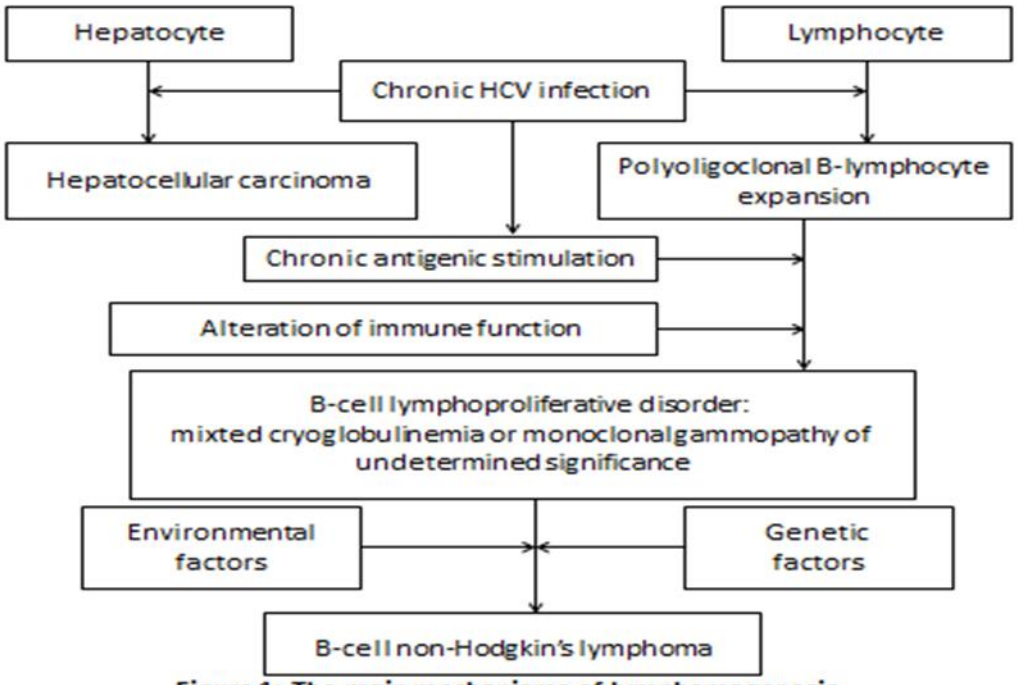

Figure 1: The main mechanisms of lymphomagenesis

4. I corrected the grammatical errors, in agreement with the recommendations of an authorized translator.

3 References and typesetting were corrected.

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

Sincerely yours,

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