

Hepatitis C Virus– Associated Non-Hodgkin Lymphomas

Biology, Epidemiology, and Treatment

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KEYWORDS

- Hepatitis C virus • Marginal zone lymphoma • Non-Hodgkin lymphoma
- Direct antiviral agents

KEY POINTS

- Eradication of hepatitis C virus (HCV) in indolent non-Hodgkin lymphomas (NHLs), especially in marginal zone lymphomas (MZLs), determines the regression of the hematological disorder in a significant fraction of cases.
- Because direct antiviral agents (DAAs) show an excellent profile in terms of efficacy, safety, and rapid onset of action, these drugs can be used in any clinical situation and the presence of any comorbidities.
- To avoid the progression of the NHL, despite HCV eradication, antiviral therapy should be provided as soon as the viral infection is discovered; before that, the chronic antigenic stimulation determines the irreversible proliferation of neoplastic B cells.

INTRODUCTION

A few years after its discovery, it became evident that HCV was able to cause not only acute liver diseases and chronic liver diseases (CLDs) but also several extrahepatic disorders. The chronic HCV infection is often associated with several rheumatological and autoimmune diseases,^{1–6} among them the most common is mixed cryoglobulinemia (MC).^{7,8} This disease is characterized, clinically, by the presence of fatigue, palpable purpura (usually on the legs), and arthralgia and, biologically, by detectable serum levels of immunoglobulins able to precipitate at a low temperature. For years,

The authors have nothing to disclose.

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MC had been considered a rheumatic disease because the histologic lesions are secondary to vasculitis, which is determined by the deposition of immunocomplexes in small and medium vessels.⁹⁻¹¹ After the availability of anti-HCV antibodies tests, more than 90% of patients affected by MC resulted were carriers of HCV infection,¹²⁻¹⁴ whereas only an insignificant fraction of the anti-HCV antibodies tests was positive for HBV infection¹⁵ or without any virologic markers and, therefore, considered as “essential”. During 1990, accurate studies on the clinical aspects and the biological characteristics of MC revealed that this disease could be regarded as a small lymphoproliferative disease because a monoclonal B-cell population was detectable in each case, including peripheral mononuclear cells.¹⁶ The B-cell monoclonality was present not only in cryoglobulinemic patients but also in a small fraction of cases of HCV hepatitis without any clinical feature of the syndrome and dosable level of cryoglobulins. This indicates that these cases show an intermediate or prodromic phase of the disease and, therefore, that the virus seems the true culprit of the MC. How an RNA virus, unable to integrate into DNA of the host, is capable of determining a lymphoproliferative disease was an intriguing question for researchers worldwide.

BIOLOGY OF HEPATITIS C VIRUS-POSITIVE LYMPHOPROLIFERATIVE DISORDERS

The HCV genome consists of a positive single-stranded RNA molecule enveloped by a lipid bilayer within which 2 different glycoproteins are anchored.¹⁷ The viral genome has 3 regions: (1) a short 5' noncoding region with 2 domains: a loop structure involved in HCV replication and the internal ribosome entry site, the region responsible for attachment of the ribosome and polyprotein translation¹⁸; (2) a large, single open reading frame of approximately 9000 nucleotides, which encodes a single polyprotein precursor that is subsequently processed by host and viral proteases into at least 3 structural and 7 nonstructural proteins with various enzymatic activities; and (3) the 3' nontranslated region endowed with high variability in the length and structure. The virus shows a high genetic diversity because, like other RNA viruses, the RNA-dependent RNA polymerase lacks a 3'-5' exonuclease with proofreading activity for removal of the misincorporated bases. Therefore, the viral replication is error-prone, and this determines a large number of variants in the same host (quasispecies virus population) with unsolvable problems for the host immune system.¹⁹ The taxonomy of HCV is complicated because the virus, by the nucleotide sequence, is classified into 6 genotypes, which show different geographic distribution, and, in addition, each genotype contains a variable number of subtypes. At the nucleotide level, the genotypes differ from each other by 31% to 33%, whereas subtypes differ from each other by 20% to 25%.²⁰ The peculiar characteristic of HCV is the ability to infect not only the liver cells but also the lymphocytes²¹ and, likely, other cells and tissues. This characteristic is due to liver cells and lymphocytes sharing the same HCV receptor, the CD81.^{22,23} This transmembrane molecule is a tetraspanin expressed on the surface of various cell types, including B cells, T cells, and natural killer (NK) cells. On human B cells, CD81 forms a costimulatory complex with CD19 and CD21, and the coligation of the B-cell antigen receptor (BCR) with any of the components of this costimulatory complex lowers the threshold for BCR-mediated B-cell activation/proliferation.²⁴ CD81-mediated activation differs from any other B-cell stimuli because it induces preferential proliferation of naïve B cells. Also, the chemokine receptor CXCR3 is up-regulated on B lymphocytes activated by CD81, whereas it is expressed at low levels after different stimulating substances.^{25,26} This interaction between HCV and the immune system could be the basis to explain the immunologic and lymphoproliferative disorders frequently found in chronic HCV infections. The potential

mechanisms of a virus for determining the lymphomas are 3: (1) active replication of the virus in the lymphocytes with abnormal regulation of several cellular genes, (2) a hit-and-run mechanism, and (3) chronic antigenic stimulation.

Whether HCV can replicate inside B cells is still a matter of debate. Some investigators found HCV-RNA–negative strands (ie, the viral replicative intermediates) in peripheral mononuclear cells,²⁷ in neutrophils,²⁸ and in CD34⁺ stem cells,²⁹ but not all researchers obtained the same results.³⁰ The HCV replication in vitro has been demonstrated in cell lines of NHL infected by the virus.³¹ Because there is in vitro evidence that some viral proteins can induce NHL in transgenic mice,³² the active viral replication in B cells could be the main mechanism of lymphomagenesis of HCV. There are, however, some perplexities on this mechanism: all studies agree on the absence of viral replication in the tissue of HCV-positive NHL.²⁹ Moreover, the transgenic mice developed follicular or large cell lymphomas, 2 histologic subtypes not usually found in HCV-related NHL.

There is some evidence that viral replication inside the cells is not necessary for determining their neoplastic transformation.³³ Viral genomes either inserted into the cellular DNA or co-replicating with it in episomal form can be lost from neoplastic cells.³⁴ The hit-and-run mechanism indicates that the transient acquisition of a complete or incomplete viral genome may be sufficient to induce malignant conversion of host cells.³⁴ Viral oncoproteins can also cause epigenetic dysregulation, thereby reprogramming cellular gene expression in a heritable manner and, after determining these changes in the gene expression pattern, the genomes of viruses may be completely lost. Two herpesviruses (Epstein-Barr virus and the Kaposi sarcoma herpesvirus) are involved in human neoplastic diseases. Epstein-Barr virus is associated with nasopharyngeal carcinoma, with post-transplant lymphoproliferative diseases, and with a subset of Hodgkin lymphoma.³⁵ Kaposi sarcoma herpesvirus is associated not only with the Kaposi sarcoma but also with primary effusion lymphoma³⁶ and with a fraction of Castleman disease.³⁷ These 2 viruses persist as episomes in the tumor cells and the episomes, although bound to cellular chromatin, are not continuous with cellular DNA. These episomes can be lost during cellular replication, but their loss has not been associated with the loss of the malignant phenotype.³⁴ It is likely that chromosomal translocations and point mutations, induced by the virus, are the driving force for the neoplastic proliferation independently from the presence of the virus. This hit-and-run mechanism has been suggested for HCV; some investigators found that HCV in vitro is able to induce mutations in several genes involved in cellular replication, such as p53, bcl-6, and β -catenin.^{38,39} The possibility that HCV could be able to induce a mutator phenotype was not confirmed by other researchers either in vitro or in lymphocytes obtained from patients chronically infected by HCV.⁴⁰

The possibility that chronic antigen stimulation could be able to determine NHL is indicated by the well-established pathogenetic link between the chronic *Helicobacter pylori* (HP) infection and the development of mucosa-associated lymphoid tissue (MALT) gastric lymphoma⁴¹; in addition, the regression of the MALT lymphoma after HP eradication makes this possibility appealing.⁴² Similarly, several reports showed the regression of B-cell monoclonality after HCV eradication with antiviral therapy.^{43,44} Not only clinical but also molecular data are in accord with the theory of the chronic antigen stimulation as the driving force for the development of the HCV-associated NHL. Because NHL arises after a long-lasting time of infection, it is likely that persistence of the virus determines chronic stimulation of B cells through the CD81, leading to polyclonal expansion of these cells that can evolve into an oligoclonal and finally monoclonal expansion. The binding of HCV E2 protein with

CD81 is able to activate the JNK pathway and, as a consequence, B-cell proliferation.

The findings of somatic hypermutations in immunoglobulin genes in some HCV-positive immunocytomas is in line with this theory. The report of preferential expression of VH51p1 associated with the VLkv325 gene combination indicates that a subtype of B lymphocytes seems implicated in chronic HCV infection, thus explaining the association between HCV and some specific low-grade or intermediate-grade NHLs.⁴⁵ Throughout the years, several studies supported the hypothesis that some viral proteins could act as antigens, leading to B-cell proliferation and the development of NHL. Some investigators, sequencing clonal variable regions of the immunoglobulin genes, demonstrated nonrandom use of the VH segments.⁴⁶ Other investigators found restricted expression of VH and VL genes in both MC and NHL.⁴⁷ Moreover, Quinn and coworkers⁴⁸ were able to demonstrate that the BCR obtained from 2 cases of HCV-positive diffuse large B-cell lymphomas was able to bind the E2 protein of HCV. Even a single rare case of HCV-positive plasma cell leukemia showed a monoclonal IgG against an HCV protein.⁴⁹ Altogether these findings support the hypothesis that HCV-NHLs are antigen-driven, as occurs in HP-triggered gastric MALT lymphomas.⁵⁰

Why a fraction of HCV-positive patients develop MC that evolves to NHL is not clear. There might be additional factors able to transform the benign lymphoproliferation of MC toward an overt NHL. In this field, it can only be assumed that several pathways can mediate the oncogenetic transformation. Some investigators⁵¹ indicated interleukin 6 as a potential element able to contribute to the development of NHL. This interleukin has a strong stimulatory effect on B cells, and it is released in several infections or inflammatory conditions.⁵² Therefore, other stochastic factors (bacterial or viral infections, traumas, and additional diseases) could determine the progression of the HCV-related lymphoproliferation toward an NHL. Other investigators found that B-lymphocyte stimulatory factor (B-Lys) is overexpressed in HCV-MC and in NHL.^{53,54} B-Lys is a good candidate as oncogenetic factor because this substance has many actions on B cells and not only increases the immunoglobulins production but also is able to activate several pathways involved in B-cell survival and proliferation, such as nuclear factor κ B (NF- κ B)⁵⁵ and extracellular signal-regulated kinases (ERK).⁵⁶ At present, however, it is not clear whether B-Lys overexpression is a mere consequence of HCV replication or is an independent cause of the progression of HCV lymphoproliferative disorders. The overexpression of bcl-2 protein could be considered the second hit, able to transform the lymphoproliferation in overt lymphoma because high levels of this antiapoptotic protein have been found in liver or marrow lymphocytes of patients affected by HCV-positive MC.^{57,58} The overexpression of bcl-2 is a common finding in follicular lymphomas, where it is generally (80%) due to a reciprocal 14:18 rearrangement. In these cases, the bcl-2 gene on chromosome 18q21 is coupled with the immunoglobulin heavy chain gene on chromosome 14q32.⁵⁹ Thus, bcl-2 is activated, and the cells bearing this translocation express high levels of bcl-2 protein. As expected, the 14:18 translocation was found in the peripheral mononuclear cells of a significant fraction of patients with MC (75%), especially in patients with type II MC (85%). This cytogenetic alteration, as well as bcl-2 overexpression, was not more detectable in the patients responding to interferon antiviral therapy. In the relapsers, however, the 14:18 translocation was again found after a variable time after the interruption of treatment, showing a behavior overlapping with HCV-RNA.⁶⁰

Recently, the mutation in the MYD88 gene, resulting in a substitution of leucine with proline at amino acid 265, has been identified in a fraction of patients affected by HCV-positive MC (Pozzato G and colleagues, 2017, unpublished data). The L265P MYD88

mutation is detected in almost all cases of Waldenström macroglobulinemia⁶¹ and in lymphoplasmacytic lymphomas with an IgM monoclonal gammopathy.⁶² In MC, the serum immunocomplexes are formed by polyclonal IgG and by monoclonal IgM (endowed with rheumatoid factor activity). Therefore, it is not surprising to find the MYD88 mutation, especially in the cases of a high level of monoclonal IgM. Many years ago, however, the possible relationship between HCV and Waldenström macroglobulinemia had been hypothesized.^{63–65} The L265P MYD88 mutant enhances NF- κ B signaling through increased binding to phosphorylated Bruton tyrosine kinase (BTK).⁶⁶ Finding this mutation could be important regarding therapeutic approaches because recently an inhibitor targeting factors downstream of L265P MYD88 signaling has become available the BTK inhibitor ibrutinib.⁶⁷ This new drug, developed for chronic lymphocytic leukemia (CLL), was shown to have an excellent efficacy in Waldenström macroglobulinemia⁶⁸ and it is likely that it could be useful even in refractory MC bearing the MYD88 mutation.

THE EPIDEMIOLOGY OF HEPATITIS C VIRUS–NON-HODGKIN LYMPHOMA

The first studies describing the possible association of HCV with NHL were published in 1994. These studies recorded the prevalence of anti-HCV antibodies in small unselected series of patients affected by NHL⁶⁹ or described the hematological characteristics and the long-term follow-up of cases affected by MC.⁷⁰ These findings were not a novelty because the first historical cases of MC reported by Melzer and colleagues⁹ and by Brouet and colleagues¹¹ were considered malignant lymphoproliferative disorders, given the presence of lymphadenopathy at presentation, whereas others developed lymphomas several years after the onset of purpura.⁷¹ The possibility, however, that a virus could be the cause of hematological, neoplastic disorders was an outstanding finding. Following this line of thinking, in the next years, many investigators addressed the possible association between HCV and NHLs in studies, including a large number of cases with proper control groups in the general population.^{72,73} These first epidemiologic data supporting the association of HCV and NHLs originated mainly from Italy, where the prevalence of HCV infection is high, especially in the South.^{74,75} Because these findings were not confirmed by researchers of other European countries,^{76–78} the relationship between HCV and NHL was thought secondary to the high prevalence of HCV in the general population and, therefore, confined to the less industrialized areas of the world. In addition to the HCV prevalence in the general population, the different results should be secondary to different enrollment modalities. The presentation of HCV-NHL is different from standard NHL, because these NHLs are usually extranodal lymphomas, involving the peripheral blood, bone marrow, spleen, and liver, thus complicating the diagnostic procedures and pathologic interpretation of histology or the imaging methods findings. In the past 20 years, many articles have been published from Europe, America, and Asia on this topic. At present, more than 10,000 cases of NHL have been evaluated for HCV infection worldwide, and several meta-analyses have been published.^{79–81}

As some investigators suggested after the first epidemiologic articles, HCV and NHL seem closely associated in some countries, independently from the crude HCV prevalence in the general population. In Italy, 18 full-length articles have been published of 2668 NHL cases, showing a prevalence of HCV infection ranging from 8.9% to 37.1%, with a mean of 19.8%.^{82–91} At least 3 of them were multicenter (21 cities involved) or case-control studies were showing an odds ratio (OR) ranging from 2.6 to 4.3. On the contrary, in Northern Europe (United Kingdom and Scandinavia) the epidemiologic studies^{77,92,93} did not find any HCV-positive patients (0%). Because in those countries

the HCV prevalence is low (0.34%–1.0%) but not zero, a small amount of NHLs positive for HCV should have been found. These findings could indicate that the ability of HCV to cause NHL shows a different geographic distribution with higher prevalence in the countries of the Mediterranean basin compared with Northern Europe.

The reports from North America confirm these findings because the 2 articles from Canada show a low incidence of HCV infection (2.3% and 0%),^{94,95} mirroring the findings from the United Kingdom, whereas 2 studies performed in Los Angeles, where more than 50% of the cases are in Hispanic people, the prevalence of HCV infection is high (11.5% and 21.7% in 312 NHLs and 120 NHLs, respectively).^{96,97}

The results of the epidemiologic studies coming from Japan are particularly difficult to compare with those performed in Western countries because in that clustered population the distribution of NHL subtypes is different (low prevalence of follicular lymphomas) whereas other B-cell neoplastic diseases, like CLL, are nearly absent. Despite this, at least 7 articles from 1996 to 2002^{98–104} documented a prevalence of HCV infection, ranging from 5.7% to 22.2% in 771 NHLs (mean 11.3%). Because 3 studies were case control, the OR was calculated, indicating a value from 2.0 to 3.1. These findings are in contrast to the absence of the B-cell monoclonality usually found in European cases affected by HCV¹⁰⁵; no cases of MC type II have been found in Japanese HCV-infected patients. The absence of the prodromic phase characterized by a small monoclonal population of B lymphocytes in peripheral blood argues against the possibility of the relationship between HCV infection and NHL, in contrast with the epidemiologic studies.

In China, the HCV prevalence in the general population ranges from 1.6% to 0.4%,^{106–108} whereas in NHL it seems to be 1.8%. In aggressive NHL, the prevalence is similar to that found in the general population (1.35%) whereas it is higher in indolent NHL (1.9%). In China, MC is a rare entity and only sporadic cases of type II MC have been described.¹⁰⁹

The authors recently published an updated meta-analysis on HCV and NHL,¹¹⁰ including not only published studies but also those with at least 1 of the following fulfilled conditions: (1) gender-adjusted and age-adjusted relative risk (RR), (2) cases and controls matched by age and gender, and (3) measures of age (mean or median or distribution) and gender ratio in cases and controls with evidence of good comparability of the 2 groups. According to these criteria, 19 case-control studies on HCV and NHL were selected, including 9038 cases and 12,224 controls. The pooled RR was 2.4 (95% CI, 2.0–3.0), and significantly elevated RRs were found in 11 studies. Overall RR estimation was 2.3 (95% CI, 1.8–2.9) with no significant heterogeneity between study designs. The authors concluded that HCV infection might be associated with an approximately 2.5-fold increase in risk of B-cell NHL.

THE TREATMENT OF HEPATITIS C VIRUS–ASSOCIATED NON-HODGKIN LYMPHOMA

The HCV-positive NHLs are heterogeneous in terms of histologic features: the most common HCV-related NHLs are the MZLs (indolent), but several diffuse large cell lymphomas (aggressive) and some mantle cell lymphomas (very aggressive) are reported. When an HCV-NHL is referred to a hematologist, several questions should be addressed. First, is NHL secondary to HCV infections or is the virus only a comorbidity? The second question is, which is the best therapeutic approach: antiviral therapy or chemotherapy?

To answer the first question, hematologists should consider that HCV-related NHLs show some histologic, clinical, laboratory, and molecular characteristics. Histologically, the most common types of HCV-NHL are lymphoplasmacytic, primary nodal

marginal zone, splenic marginal zone, and MALT marginal zone, whereas other histotypes are less closely associated with HCV.¹¹¹ Clinically, the course of the HCV-NHLs are indolent and often linked to the longstanding presence of MC.⁷⁰ From a biological point of view, the HCV-NHLs often show a monoclonal IgMk (IgM with k light chain) component and the presence of several autoantibodies. From a molecular point of view, some investigators describe the presence of the bcl-2/IgH translocation (although not confirmed by others)^{57,58} and others the MYD88 mutation.

To choose the best therapeutic strategy, several factors should be taken into consideration. The first factor is the tumor burden: in the presence of large nodal or extranodal masses, chemotherapy becomes the first choice; on the contrary, when the tumor burden is low (usually mild bone marrow lymphoid infiltration associated with an enlarged spleen), antiviral therapy could be more appropriate. A second factor is the course of the disease: when the course is indolent and the lymphoma is discovered incidentally, antiviral therapy could be more attractive, whereas if a patient shows progressive and rapid node or spleen enlargement, chemotherapy is again the best choice. A third important factor is the presence and the quality of clinical symptoms: in the case of the symptoms that are traditionally NHL related (nocturnal sweating, weight loss, and fever), chemotherapy is indicated, while in the case of the symptoms that are MC related (purpura, vasculitis, arthralgia, and so forth), antiviral treatment could be more indicated.

Before starting any therapy, HCV-related NHL should always be investigated for the possible presence of an underlying CLD. This means that these patients should undergo a complete hepatological evaluation, including ultrasonography and, if indicated, endoscopy and liver biopsy. In patients showing advanced CLD or with severe portal hypertension or showing impending liver failure, chemotherapy as well as interferon-based antiviral therapy is contraindicated. In these cases, the immunotherapy with anti-CD20 antibodies could be the only therapeutic option. The presence of HCV replication, that is, detectable levels of HCV-RNA, without CLD, cannot be considered a contraindication for chemotherapy. In fact, when HCV-MC patients undergo intensive immunosuppressive therapies, including anti-CD20 therapy, liver function never worsens despite increased HCV-RNA levels.^{112,113} Some articles confirm this point of view, in that acute hepatitis due to the reactivation of HCV has been noticed in a very small group of Italian HCV-RNA-positive NHL after chemotherapy,¹¹⁴ and these data have been confirmed in larger cohorts of patients.^{115,116}

The traditional antiviral therapy for HCV infection had been based for decades on the use of interferon-alfa (IFN) and ribavirin (RBV). From 1996 to 2013, approximately 110 cases of HCV-NHL had been treated with the combination therapy, but different outcomes are reported by various investigators. These differences can be explained by the very small number of enrolled patients: 8 articles reported a single case and only 4 articles had more than 10 cases (**Table 1**). In addition, different histotypes were enrolled with obvious different response rates. Moreover, several investigators included cases of liver disease whereas others excluded these cases, and, finally, the presence of MC is not recorded by all the investigators. To increase the complexity of the results, a fraction was treated with IFN as monotherapy, another fraction with IFN and RBV, and another group with pegylated IFN (PEG-IFN) and RBV. The different antiviral efficacy of these 3 regimens increases the difficulty to interpret these results. At least 3 studies reported rather homogeneous results because all the patients were treated with the same antiviral regimen (PEG-IFN and RBV), allowing better interpretation of the data. In all 3 articles, the hematological response significantly ($P < .005$) correlated with the disappearance of HCV-RNA, and the cases of virologic relapse

Table 1
Main studies concerning interferon-based antiviral treatments in patients with hepatitis C virus-associated lymphomas (studies with fewer than 10 cases are not reported)

Investigators	Cases (no.)	Type of Therapy	Histology of Non-Hodgkin Lymphomas	Mixed Cryoglobulinemia	Virologic Response	Non-Hodgkin Lymphomas Response
Tursi et al, ¹¹⁷ 2004	16	IFN + RBV	MZL	Not reported	11 SVR (69%)	13 CR (81%) 2 PR (11%)
Saadoun et al, ¹¹⁸ 2005	18	IFN + RBV (8) PEG-IFN + RBV (10)	SPVL (18)	18	14 SVR (78%)	14 CR (78%) 4 PR (22%)
Mazzaro et al, ¹¹⁹ 2009	18	IFN + RBV (8) PEG-IFN + RBV (10)	SPVL (1), LPL (16) FL(1)	13	3 SVR (38%) 6 SVR (60%)	3 CR (38%) 2 PR (25%) 6 CR (60%) 2 PR (20%)
Vallisa et al, ¹²⁰ 2005	13	PEG-IFN + RBV	FL (1) LPL (4) MZL (8)	5	7 SVR (54%)	7 CR (54%) 2 PR (15%)

Abbreviations: CR, complete response; FL, follicular lymphoma; LPL, lymphoplasmacytic lymphoma; PR, partial response; SPVL, splenic MZL with villous lymphocytes; SVR, sustained virologic response.

also had NHL recurrence a few months later. Given better antiviral efficacy of these treatment regimens, the relapse rates were lower in these 3 studies (30%) than those of the previously reported relapse rates.^{117–120}

The development of HCV therapy has progressed significantly, however, in the past few years. The traditional association of PEG-IFN and RBV has now been abandoned after the introduction of the new DAAs. These drugs include inhibitors of the HCV NS4/4A protein (simeprevir, paritaprevir, and grazoprevir) of the NS5A protein (ledipasvir, daclatasvir, ombitasvir, and elbasvir) or the viral polymerases (sofosbuvir and dasabuvir).¹²¹ Although with different mechanisms of action, all these drugs share the same profile of high efficacy associated with low side effects. The published studies of these new DAAs indicate a remarkable eradication rate, ranging from 90% to 100% in any stage of the liver disease, with the exception of rare cases of decompensated cirrhosis. The efficacy of these new DAAs regarding the extrahepatic manifestations of HCV infection is largely unknown because few publications were available on this topic. Until now, a small series of articles has reported single cases of MC or NHL regression after HCV eradication with the new DAAs,^{122–124} whereas only 3 articles have shown a large number of cases.^{125–127} In these articles, despite the eradication of HCV in near the totality of cases, not all HCV-RNA-negative patients obtained the complete recovery from the clinical symptoms together with the persistence, although attenuated, of the biological characteristics of the MC. Zignego and coworkers¹²⁸ noticed that in 2 cases of a small monoclonal B-cell population in peripheral blood, the HCV eradication did not determine the disappearing of the B-cell monoclonality. Similar findings are described in another case report.¹²⁹ Recently, Arcaini and colleagues¹³⁰ described the efficacy and safety of the therapy with the new DAAs in a significant number of indolent NHLs collected in several centers of Italy and France. This report confirms the high efficacy of DAAs on HCV, because the totality of cases (except 1 single patient with decompensated cirrhosis) obtained the sustained virologic response, including in patients who had undergone previous chemotherapy and/or previous interferon-based antiviral treatments. The hematological response seems less satisfactory because only a fraction of patients obtained the complete remission of the NHL and most patients who obtained a partial remission relapsed or had a progression of the disease requiring chemotherapy or immunotherapy. Although the methods for determining the responses are lacking, the results are interesting, confirming the good response rate of the MZLs both nodal and extranodal. On the contrary, no response was observed in the 4 cases of small lymphocytic lymphoma (SLL)/CLL. These findings support the hypothesis of different pathophysiologic events between SLL/CLL and MZL. As a consequence, the presence of HCV in SLL/CLL should be considered fortuitous without any pathogenetic correlation. The DAA therapy was well tolerated and its toxicity was negligible. The absence of side effects is crucial in this setting, especially in cases already treated or prone to undergo chemotherapy or immunochemotherapy. The efficacy of DAAs in eradicating NHL as well as HCV-RNA, at least in MZL, confirms the pathogenetic role of HCV and supports the hypothesis of a lymphomagenesis induced by the chronic antigenic stimulation. Unfortunately, in a large fraction of patients, the neoplastic hematological disease progresses despite the disappearance of HCV-RNA. It is likely that in these cases, the B-cell proliferation became independent from virus replication. As suggested by Zignego and colleagues,¹²⁸ the persistence of MC after HCV eradication is conceivable because the DAAs lack any immunomodulatory or anti-proliferative effect. Alternatively, the persistence of the symptoms can be due to the short follow-up of these patients.

In conclusion, eradication of HCV in indolent NHL, especially in MZL, determines the regression of the hematological disorder in a significant fraction of cases. Because DAAs show an excellent profile in terms of efficacy, safety, and rapid onset of action, these drugs can be used in any clinical situation and presence of any comorbidities. To avoid the progression of the NHL, despite HCV eradication, antiviral therapy should be provided as soon as the viral infection is discovered; before that, the chronic antigenic stimulation determines the irreversible proliferation of neoplastic B cells.

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