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REVIEW

Antiviral therapy of hepatitis C as curative treatment of indolent B-cell lymphoma

Michele Merli, Giuseppe Carli, Luca Arcaini, Carlo Visco

Michele Merli, Division of Hematology, University Hospital Ospedale di Circolo & Fondazione Macchi, University of Insubria, 36100 Varese, Italy

Giuseppe Carli, Carlo Visco, Department of Cell Therapy and Hematology, San Bortolo Hospital, 36100 Vicenza, Italy

Luca Arcaini, Department of Molecular Medicine, University of Pavia, 27100 Pavia, Italy

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Correspondence to: Dr. Carlo Visco, Department of Cell Therapy and Hematology, San Bortolo Hospital, Via Rodolfi 37, 36100 Vicenza, Italy. carlovisco@hotmail.com
Telephone: +39-444-753626
Fax: +39-444-753626

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Abstract

The association of hepatitis C virus (HCV) and B-cell non-Hodgkin lymphomas (NHL) has been highlighted by several epidemiological and biological insights; however the most convincing evidence is represented by interventional studies demonstrating the capability of antiviral treatment (AT) with interferon (IFN) with or without ribavirin to induce the regression of indolent lymphomas, especially of marginal-zone origin. In the largest published retrospective study (100 patients) the overall response rate (ORR) after first-line IFN-based AT was 77% (44% complete responses) and responses were sustainable (median duration of response 33 mo). These results were confirmed by a recent meta-analysis on 254 patients, demonstrating an ORR of 73%. Moreover this analysis confirmed the highly significant correlation between the achievement of viral eradication sustained virological response (SVR) and hematological responses. Two large prospective studies demonstrated that AT is associated with improved survival and argue in favor of current guidelines' recommendation of AT as preferential first-line option in asymptomatic patients with HCV-associated indolent NHL. The recently approved direct-acting antiviral agents (DAAs) revolutionized the treatment of HCV infection, leading to SVR approaching 100% in all genotypes. Very preliminary data of IFN-free DAAs therapy in indolent HCV-positive NHL seem to confirm their activity in inducing lymphoma regression.

Key words: Non-hodgkin lymphomas; Hepatitis C virus; Antiviral therapy; Interferon; Ribavirin; Sofosbuvir; Direct-acting antiviral agents; Marginal zone lymphomas

Core tip: In the last decade many clinical studies demonstrated that front line antiviral therapy (AT)

with interferon (IFN) and ribavirin, is able to induce a 70%-75% response rate in patients with hepatitis C virus (HCV)-associated indolent non-Hodgkin lymphoma who do not need immediate conventional treatment. Hematological response was durable, and invariably related to the viral eradication. International guidelines indicate that AT should be the treatment of choice in such patients. Very preliminary data about the use of the new direct-acting antiviral agents (DAAs) suggest a similar activity in inducing lymphoma response. We discuss available literature about IFN-based AT and preliminary experiences with DAAs in the treatment of HCV-associated indolent lymphomas.

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INTRODUCTION

The association between hepatitis C virus (HCV) and B-cell non-Hodgkin lymphomas (NHL) is now widely accepted, as a result of the large body of evidences from epidemiological, biological and especially therapeutic studies carried out in the last 15 years. Among B-cell NHL indolent subtypes, HCV has been consistently associated with marginal-zone lymphomas (MZL), while within aggressive histotypes the highest correlation has been found with diffuse large B-cell lymphomas (DLBCL)[1-3].

The most convincing argument in favor of an etiological link between HCV and specific histotypes of B-cell NHL is indeed represented by the highly frequent success of HCV-directed antiviral therapy (AT) in inducing lymphoma regression in patients with HCV-positive indolent lymphomas. Across all the published studies, lymphoma response has been significantly related to the obtainment of viral eradication. As a result, current international guidelines support the use of front-line AT in asymptomatic patients with HCV-associated indolent lymphomas who do not require immediate conventional immune-chemotherapy approach[2].

Many pathogenetic models have been proposed to elucidate possible mechanisms of HCV-related lymphomagenesis and consequential lymphoma regression induced by AT-induced viral eradication: The most accepted and supported by experimental evidences rely on chronic antigenic stimulation of lymphocyte receptors by viral antigens resulting in B cells proliferation, similarly to the *Helicobacter pylori*-induced gastric MALT lymphoma ("antigen-driven proliferation")[1] and, alternatively, on HCV replication inside B-cells with oncogenic effects mediated by intracellular viral proteins HCV ("intracellular viral replication"). Also from the biological point of view a great expectation is represented by the introduction in HCV-related B-cell non-Hodgkin lymphomas (B-NHL) of the new direct-acting antiviral agents (DAAs) that, after nearly 25 years of interferon (IFN)-based therapy, are revolutionizing HCV treatment by inducing nearly 100% sustained virological responses (SVRs). As the cytostatic effect of IFN could not be completely ruled out, the evaluation of new "IFN-free" AT as curative-intent primary treatment of HCV-associated indolent lymphomas may ultimately clarify the real grade HCV-dependency of different lymphoma subtypes. Recent case reports seem to confirm the efficacy of different new schedules of IFN-free AT in inducing lymphoma regression, however more large and possibly prospective series are needed to clarify this issue. If this would be proven by prospective studies, IFN-free AT may be regarded as a real "chemo-free" targeted therapy for HCV-related indolent lymphomas.

The aim of this paper is to summarize the up-to now reported experiences with both IFN-based and new DAA-based AT delivered as curative treatment in patients with HCV-associated indolent B-NHL.

HCV INFECTION AND INDOLENT LYMPHOMAS

Epidemiological studies

It is estimated that 3% of the world population (170 million people) is chronically infected by HCV. HCV prevalence varies consistently in different geographic areas, with lowest rates being reported in Northern Europe and Scandinavia (0.1%-0.4%) while in Italy, Egypt, Japan and southern parts of United States, prevalence estimates exceeds 2%. HCV has been linked to a spectrum of lymphoproliferative disorders with or without cryoglobulinemia[2]. The first evidences about the link between HCV and B-NHL were established by epidemiologic studies. A recent updated meta-analysis including 19 case-control studies (9038 cases and 12224 controls) and 4 cohort studies confirmed the previous reported data of 2.0-2.5-fold increased risk of developing B-cell NHL in HCV-infected patients (2.4 relative risk in case-control studies and 2.0 in cohort studies), with higher risk in countries with higher HCV prevalence[3]. For instance, in countries with high HCV prevalence like Italy (4.4%; 1.6% in the North and 7.3% in the South)[4], the fraction of B-cell NHL attributable to HCV may be estimated close to 10%, while in countries with low prevalence as in Northern Europe only < 1% of B-NHL may be considered to be linked to HCV[5]. Concerning specific NHL subtypes, the large international "*Interlymph*" study reported a significant association of HCV infection and MZL (OR = 2.47), DLBCL (OR = 2.24), and lymphoplasmacytic lymphoma (LPL, OR = 2.57)[6]. Moreover, retrospective studies reported a high HCV seroprevalence among patients features suggesting

the transformation from a previously unrecognized low with MZL and DLBCL[11-13]. Notably, many studies focusing on HCV-positive DLBCL showed histologic as well as molecular -grade lymphoma, mainly MZL[12-15].

An interesting confirmation of the association of HCV and B-cell NHL may be argued by a Japanese large cohort prospective study evaluating the differential rate of NHL development in two cohorts of HCV-infected patients treated (n = 2701) or not (n = 501) with IFN-based AT. While in patients who received IFN without obtaining SVR the rate of new diagnosis of NHL resulted similar to those who did not receive IFN (0.4%, 1.5% and 2.6% at 5, 10 and 15 years, respectively), no patient obtaining SVR after AT developed NHL. In other words, the eradication of HCV infection by AT was able to prevent the development of lymphoma[16]. A confirmation of these findings was recently furnished by a Taiwanese population-based cohort study (11.679 HCV and 46716 non-HCV patients followed for 8 years). The incidence rates of NHL were significantly greater in the HCV cohort than the non-HCV cohort (37.0 *vs* 17.5 per 100000 person-years) and multivariate analysis showed that HCV infection was associated with an increased rate of NHL (HR = 2). Noteworthy, similarly to the Japanese study, the incidence rate of NHL development was 0 per 100000 person-years in HCV-patients who received IFN-based AT (n = 958) compared with 41 per 100000 person-years in the untreated group[17].

Clinical and pathological studies

In the WHO classification (2008) three MZL entities are listed[18]: SMZL, NMZL and extranodal MZL of MALT-type (MALT lymphoma). Marginal zone B-cells play an important role in various infectious and autoimmune conditions and marginal zone-related neoplasms often retain features of these cells. In addition to epidemiological studies, the association between HCV and MZL is supported by several large clinical-pathological MZL series, especially in SMZL. In a large multicentre series of SMZL from Italy HCV serology was positive in 49 out of 255 available cases (19%), who presented with more frequent presence of nodal disease, cryoglobulinemia and serum monoclonal component[7]. In 2005, French authors described a clinical trial of SMZL with villous lymphocytes, type Ⅱ mixed cryoglobulinemia and HCV infection in 18 patients[24]. NMZL is a rare entity accounting for less than 2% of NHL; in the largest published series[10], HCV serology was positive in 9 out of 38 patients (24%). Considering MALT lymphomas, a multicenter Italian study on 172 patients, pointed out the high rate of positivity of HCV serology (35%), with 92% of tested cases being positive for HCV-RNA. Interestingly, a prominent prevalence of HCV infection was reported in three peculiar MALT lymphoma sites: Salivary glands (47%), skin (43%) and orbit (36%)[10]. At this regard a new peculiar clinical and pathological entity of extranodal MALT MZL of the skin has been characterized in 12 HCV-positive patients, who presented single or multiple subcutaneous "lipoma-like" nodules and displayed indolent clinical course and responsiveness to AT[25]. LPL and Waldenström macroglobulinemia have been associated with HCV infection and mixed cryoglobulinemia in some but not all series, perhaps related to geographic differences[26]. Follicular lymphoma (FL) and small lymphocytic lymphoma (SLL), on the contrary, have been rarely associated with HCV infection. Other residual cases of low-grade miscellaneous lymphoproliferative disorders frequently reported as low-grade "B-NHL not otherwise specified" (B-NHL NOS), characterized by exclusive bone marrow and leukemic involvement with flow cytometry features different from those of chronic lymphocytic leukemia (CLL), have been sometimes associated with HCV infection[27].

Besides reports focusing specifically on single HCV-associated histotypes of indolent NHL, two different large prospective observational studies provided a comprehensive overview of subtypes distribution and clinical picture of HCV-positive NHL. The French "ANRS Lympho-C" observational study enrolled between 2006 and 2012 116 consecutive patients with HCV infection and a new diagnosis of NHL, including 39%MZL and 39% DLBCL. Median age was 62 years, 52% had genotype 1 and 25% genotype 2. Patients with MZL had more frequently serum rheumatoid factor positivity (68% *vs* 35%) and monoclonal component (74% *vs* 44%) with respect to patients with DLBCL[28].

ANTIVIRAL TREATMENT OF HCV-POSITIVE INDOLENT LYMPHOMAS

The seminal work by Hermine *et al*[30] in SMZL with villous lymphocytes in 2002 has opened the way to several following consistent data from the literature demonstrating that AT should be considered as a reliable frontline approach in HCV-associated indolent lymphomas when there is no immediate need of conventional treatment. Such behaviour has been recommended by recently updated haematological (ESMO[31] and NCCN[32]) and hepatological (EASL[33]) international guidelines. Among specific NHL subtypes, this treatment modality has been more frequently adopted in MZL although many studies in IFN era extended the validity of this approach for all indolent histologies when associated to HCV infection. Table 1 summarizes the results of anti-lymphoma IFN-based AT experiences [with or without ribavirin (RBV)] in low-grade NHL.

On the contrary, front-line AT it is clearly insufficient in HCV-positive aggressive lymphomas and could not be considered as a curative treatment modality in this setting, in which an immediately active therapy is needed. However AT may be a logical recommendation in HCV-positive DLBCL after completion of standard

Table 1 Interferon-based antiviral treatment in hepatitis C virus-infected patients with low-grade non-Hodgkin lymphomas

	Year	No. of patients	Diagnosis	Genotypes	Cryoglobulinemia	Antiviral treatment	Virologic response	NHL response
Bauduer[35]	1996	1	MZL of MALT (oral cavity)	NA	-	α-IFN	1	1 PR
Caramaschi *et al*[36]	1999	1	MZL of MALT (salivary glands)	NA	-	α-IFN	NA	1 CR
Moccia *et al*[37]	1999	3	SMZL	NA	-	α-IFN	NA	2 CR
Patriarca *et al*[38]	2001	1	LPL	2a/2c	-	α-IFN	1	1 CR
Hermine *et al*[30]	2002	9	SLVL	NA	6	α-IFN	7	7 CR
Casato *et al*[39]	2002	1	Leukemic MZL	NA	1	α-IFN	Decreased HCV-RNA	1 CR
Pitini *et al*[63]	2004	2	SMZL	NA	-	α-IFN	2	2 CR
Tursi *et al*[64]	2004	16	MZL of MALT (stomach)	NA	-	α-IFN-2b + RBV	11/16	16 CR
Kelaidi *et al*[41]	2004	8	SMZL (*n* = 4)	3a (*n* = 1), 5a (*n* = 1)	8	α-IFN-2b + RBV	5 SVR, 2 PR	5 CR
			Disseminated MZL (*n* = 1)	-				
			Leukemic MZL (*n* = 1)	1b				
			MZL of MALT (*n* = 2) (1 duodenus; 1 ileus)	4c/4d				
Vallisa *et al*[42]	2005	13	SMZL (*n* = 4)	1b (*n* = 2), 2b (*n* = 1)	5	Peg-IFN + RBV	7 SVR, 1 PR	7 CR, 2 PR
			NMZL (*n* = 2)	2a/2c (*n* = 1), 1b (*n* = 1)				
			MZL of MALT (*n* = 2)	1b (*n* = 2)				
			FL (*n* = 1)	2a				
			LPL (*n* = 4)	2a/2c (*n* = 1), 1b (*n* = 1), na (*n* = 2)				
Svoboda *et al*[65]	2005	1	MZL of MALT (salivary gland, liver)	2b	-	Peg-IFN + RBV	1	CR
Saadoun *et al*[24]	2005	18	SLVL	1 (*n* = 7) 2 (*n* = 4) 3 (*n* = 1) 4 (*n* = 1)	18	α-IFN (+ RBV in 10)	14 CR, 4 PR	14 CR, 4 PR
Paulli *et al*[25]	2009	2	Subcutaneous MZL of MALT	2a/2c, 2b	2	Peg-IFN + RBV	2 CR	1 CR, 1 PR
Mazzaro *et al*[43]	2009	18	1 SLVL	1b (*n* = 11)	13	α -IFN + RBV (*n* = 8)	9 SVR	9 CR, 4 PR
			1 FL	2a/2c (*n* = 7)		Peg-IFN + RBV (*n* = 10)		
			16 LPL					
Oda *et al*[66]	2010	1	B-NHL (liver)	2a	-	Peg-IFN + RBV	SVR	CR
Pellicelli *et al*[67]	2011	9	3 SMZL	1b (*n* = 2)	4	Peg-IFN + RBV	7 SVR	5 CR, 2 PR
			3 MZL of MALT	2 (*n* = 2)				
			1 NMZL	2a (*n* = 2)				
			2 FL	2a/2c (*n* = 3)				
Mauro *et al*[68]	2012	1	LPL	1b	1	Peg-IFN + RBV (2nd line)	SVR	CR
Arcaini *et al*[45]	2014	100	23 SMZL	1 (*n* = 37)	34	α-IFN (*n* = 33) (+ RBV in 26)	80% SVR	44% CR, 33% PR
		(1st-line)	12 NMZL	2 (*n* = 52)		Peg-IFN (*n* = 67) (+ RBV in 57)		
			25 MZL of MALT	3 (*n* = 5)				
			7 LPL	5 (*n* = 1)				
			5 FL	NA (*n* = 5)				
			1 SLL					
			27 Low-grade NHL NOS					
		34	12 SMZL	1 (*n* = 15)	10	α-IFN (*n* = 14) (+ RBV in 10)	67% SVR	56% CR, 29% PR
		(2nd-line)	2 NMZL	2 (*n* = 13)		Peg-IFN (*n* = 20) (+ RBV in 15)		
			6 MZL of MALT	3 (*n* = 2)				
			2 LPL	5 (*n* = 1)				
			7 FL	NA (*n* = 4)				
			3 SLL					
			2 Low-grade NHL NOS					

Michot *et al*[28]	2015	14 (AT alone)	14 MZL	NA	NA	Peg-IFN + RBV (n = 12)	79% SVR (AT alone)	57% CR, 21% PR
		8 (At + Rituximab)	8 MZL	NA	NA	PegIFN + RBV + 4 Rituximab (n = 8)	NA (AT + Rituximab)	38% CR, 62% PR

SMZL: Splenic marginal zone lymphoma; NMZL: Nodal marginal zone lymphoma; SLVL: Splenic lymphoma with villous lymphocytes; MZL: Marginal zone lymphoma; FL: Follicular lymphoma; LPL: Lymphoplasmacytic lymphoma; MCL: Mantle cell lymphoma; SLL: Small lymphocytic lymphoma; NHL: Non-Hodgkin lymphoma; NOS: Not otherwise specified; IFN: Interferon; RBV: Ribavirine; CR: Complete response; PR: Partial response; SVR: Sustained virologic response.

R-CHOP immune-chemotherapy with the aim to eliminate a potential lymphoma trigger and reduce the risk of relapse[14,34].

First experiences (2002-2011) in the interferon era

The majority of the initial studies reporting the use of IFN as primary lymphoma treatment in HCV-infected patients diagnosed with a lymphoproliferative disorder relied on single case reports or small case series[35-39], and included also patients with type-2 mixed cryoglobulinemia with evidence of B-cell monoclonality (IgH and/or Bcl-2 rearrangement)[40].

In 2002 Hermine *et al*[30] reported data on AT in 9 patients with splenic lymphoma with villous lymphocytes and HCV infection treated with IFN-2αb. Six patients presented also symptomatic cryoglobulinemia. Complete hematological response and SVR were observed in 7 out of 9 patients. The remaining 2 patients who did not respond were subsequently treated with IFN plus RBV and obtained HCV-RNA clearance as well as lymphoma response [one complete response (CR) and one partial response (PR)]. In contrast, none of 6 matched patients with SLVL without HCV infection treated with IFN experienced any grade of lymphoma regression.

In 2005 the same French group expanded these results in 18 patients with chronic HCV infection, mixed cryoglobulinemia and SLVL treated with IFN (+ RBV in 10). Fourteen patients (78%) obtained a CR after clearance of HCV-RNA. Two patients who obtained only a virologic PR and 2 non-responders achieved nevertheless a PR of lymphoma, with an overall response rate (ORR) of 100%[24].

Another study reported the use AT with IFN and RBV as first-line treatment in 8 HCV-positive patients with different MZL subtypes (4 SMZL with or without villous lymphocytes; 1 disseminated MZL, 1 leukemic MZL and 2 intestinal MALT-lymphomas): Overall, 5 out of 8 patients (60%) obtained a CR of lymphoma, which was related to SVR in the majority of cases[41].

Among most significant initial experiences, an Italian multicenter study reported results of AT in 13 HCV-infected patients with various low-grade B-NHL subtypes[42]. All patients received peg-IFN and RBV, 10 as first-line and 3 as second or third-line of therapy. Among 12 assessable patients, 7 achieved CR, 2 PR (ORR = 75%), 2 had stable disease (SD) and one progressed during therapy. Similarly to previous reports, hematologic responses resulted significantly associated to clearance of HCV viral load, as 7 out of 9 responders achieved prior SVR. Although number of cases was small, this study suggested for the first time that AT with peg-IFN and RBV may be equally effective also in a wide range of HCV-positive low-grade NHL subtypes other than MZL, as CRs were actually observed without significant differences in all indolent NHL histologies (2 out of 4 non-MZL and 5 out of 8 MZL).

In 2009 Mazzaro *et al*[43], reported a series of 18 patients with HCV-positive low grade B-cell NHL (16 LPL, 1 FL, 1 SLVL) treated frontline with PEG-IFN or standard IFN (plus RBV). SVR and CRs resulted higher in the group treated with PEG-IFN (6 out of 10 patients, 60%) with respect to the group treated with standard IFN (3 out of 8 patients, 37%). All the 9 patients who obtained SVR experienced also CR of lymphoma, thus confirming the previously found strict relationship between the achievement of virological and hematological CR.

Most recent studies (2014-2015)

In 2014, the Fondazione Italiana Linfomi (FIL) reported data[45] on 100 patients with HCV-positive indolent NHL (23 SMZL, 12 NMZL, 25 MALT-lymphomas, 7 LPL, 5 FL, 1 SLL, 27 indolent B-NHL NOS), all characterized by an indolent course of disease without the need to receive immediate conventional anti-lymphoma therapy, were treated with first-line AT. Thirty-three patients received IFN and 67 received PEG-IFN-based AT (with or without RBV). Six patients discontinued AT due toxicity, while 7 patients interrupted early AT due to lymphoma progression and lack of virological response. Forty-four (44%) patients achieved a CR and 33 (33%) a PR, with an ORR of 77%; 14 patients had SD. Median duration of response (DOR) was 33 months. A SVR was achieved in 80 patients (80%). Lymphoma response resulted significantly associated to the achievement of a SVR (P = 0.003) while it was not recorded a significant difference in ORR between patients with MZL or non-MZL histology (82% *vs* 70%, P = 0.3). At a median follow-up of 3.6 years, 9 patients progressed and 13 experienced lymphoma relapse after initial response to AT, with a resulting 5-year PFS of 63%. Five-year OS was 92%; only 2 patients died due to lymphoma progression.

Thirty-four patients were treated with second-line AT for relapse after a conventional first-line therapy: Among them, 19 (56%) achieved a CR and 10 (29%)

a PR (ORR 85%); a SVR was achieved in 22 patients (67%). The median DOR was 26 months and 5-year PFS was 63%.

These recent data unequivocally confirm the high rates of lymphoma regression in patients with HCV-positive indolent NHL treated with AT without significant differences between various histologies, although MZL represent the more frequent subtype. Moreover, the established association of hematological response with virological response confirms previous findings and is in accordance with the proposed pathogenetic model of chronic antigenic stimulation in HCV-positive indolent lymphoma, thus underlying the importance of virus eradication.

Another large cohort of patients with HCV-NHL (n = 116), including 45 patients with MZL, was recently published. However, of 38 patients with MZL treated with IFN-based AT, only 14 received AT alone, while 8 patients with high tumor burden were treated with AT with the addition of 4 weekly dose of rituximab, a schedule adopted from therapy of type 2 cryoglobulinemia. Among the 14 patients receiving with AT alone, 8 obtained a CR and 3 a PR (ORR 79%), while all patients treated with the combination of AT and rituximab responded (3 CR, 5 PR; ORR 100%).

A highly relevant finding confirmed independently by the two last cited studies is represented by the positive impact of AT on the prognosis of the patients with HCV-associated indolent lymphoma. The FIL "*HCV-LNH outcome survey*" included 704 consecutive HIV-negative HCV-positive patients with indolent NHL diagnosed and treated from 1993 to 2009 in 39 centres of the FIL; 134 patients received AT as first or second-line therapy, as previously described. In the whole cohort, 5-year OS was 78% and 5-year PFS was 48%. In multivariate analysis, use of AT during the patients' life (*i.e.*, as first-line or as subsequent line of therapy) had positive impact on OS. In details, in patients who performed AT the overall risk of death was significantly reduced (HR = 0.21, P = 0.014)[45]. Similarly, in the French *"ANRS Lympho-C Study"* the use of AT resulted significantly associated with improved OS in MZL at multivariate analysis (HR = 0.11)[28]. This obviously means that, at least in these unselected retrospective series, AT is able to prolong the survival of patients with HCV-positive indolent NHL and further emphasizes the validity of this treatment strategy as the cornerstone treatment of HCV-related in indolent NHL in a long-term perspective.

A recently published meta-analysis specifically evaluated this issue. The primary endpoint was the correlation between SVR and lymphoma response, while secondary endpoints were overall lymphoma response rate and differential efficacy within various histotypes. Overall, 254 patients from 20 studies were included. Overall lymphoma response rate following AT was 73% (95%CI: 67%-78%) and a strong statistical association between SVR and lymphoma response was confirmed: In particular patients obtaining SVR displayed 83% response rate compared to 53% response rate of those failing to achieve SVR (P = 0.0002). A trend towards a better response to AT in HCV-associated MZL (ORR 81%) compared to non-MZL histotypes (ORR 71%, P = 0.07) was observed. In summary, the results of this updated meta-analysis further justifies the current recommendation for AT as first-line treatment in patients who do not need immediate conventional treatment and support the hypothesis of a causal relationship of HCV and lymphomagenesis[46].

MOLECULAR FEATURES OF HCV-ASSOCIATED INDOLENT LYMPHOMAS TREATED WITH INTERFERON-BASED ANTIVIRAL TREATMENT

Only scanty data concerning molecular features of HCV-related indolent NHL, especially in the setting of AT, have been presented, mainly due to the retrospective nature and to the low number of patients analyzed in these studies.

Concerning mutational profile, no difference between HCV-positive and HCV-negative cases was found in the genomic landscape of SMZL by integrating whole-exome sequencing and copy-number analysis. In particular, rate of mutation in NOTCH pathway genes (*NOTCH2* in about 20%-40%, *NOTCH1* in about 5%, *SPEN*, *DTX1* or *MAML2*), NF-αB signaling pathway genes (*IKBKB* in about 10%, *TNAIF3* in about 5%), *KLF2* (about 20%-40%) or TP53 (about 15%) did not differ according HCV-status[47]. Interestingly the only molecular difference between HCV-positive and HCV-negative SMZL was detected by miRNA expression analysis: In particular, HCV-positive SMZL patients revealed a downregulation of the tumor suppressive miR26b[49].

From the immune-genetic point of view, many biologic studies focusing on HCV-related lymphomagenesis, demonstrated that HCV-positive NHL frequently carry signs of somatic hypermutation and preferential usage of restricted repertoire of VH (*e.g.,* V_H1-69) and VL genes (*e.g.,* V_k3-20/15)[50], suggesting a possible role of antigen selection in expansion of the B-cell clone, that would be therefore still antigen-dependent, at least until a certain postulated critical turning-point. According to this hypothesis, stereotyped B-cell receptors were found in 12% SMZL cases, including HCV-positive cases, pointing out the role of antigen selection (both HCV and non-HCV restricted) in SMZL development[51].

On the basis of the previous findings in patients with HCV-related type-Ⅱ mixed cryoglobulinemia, the first interventional studies evaluating AT in patients with NHL looked out to the achievement of molecular response. In the seminal study of Hermine *et al*[30], as well as in the subsequent report by Saadoun *et al*[24],

and in the Italian multicenter study[42], despite the achievement of clinical CR in the majority of patients, none of the patients evaluated by investigation of IgH-specific rearrangement or Bcl2/IgH translocation obtained a molecular response after AT. This finding differed from what reported in patients affected only by type Ⅱ mixed cryoglobulinemia, a benign lymphoproliferative disorder that may evolve in overt in NHL in 5%-10% of cases, where the disappearance of B-cell clones from the blood of HCV-infected patients after AT has been reported[40]. One can speculate that this differential pattern of molecular responses may be related to the more advanced stage of neoplastic transformation at molecular level of B-cells in low-grade NHL, which imply the achievement of a higher grade of antigen-independency with respected to type Ⅱ mixed cryoglobulinemia.

NEW DAAS ERA IN THE TREATMENT OF HCV INFECTION

HCV therapy is undergoing a revolution. After nearly 25 years of improvements of IFN-based therapies, enormous research efforts led ultimately to the license of a large number of new DAAs. DAAs include different classes of antiviral agents that inhibit HCV viral-specific non-structural (NS) proteins: Protease inhibitors (NS3), NS5A replication-complex inhibitors, nucleoside and non-nucleoside NS5B (viral RNA-polymerase) inhibitors[52].

More than 90% of infections were reported to be cured in phase Ⅱ and Ⅲ trials, with or without peg-IFN and/or RBV. A plethora of new DAA with differential activity across different HCV genotypes is undergoing clinical investigation, with the aim to develop IFN- and possibly RBV-free oral regimen with efficacy approaching 100% and without significant toxicity.

Sofosbuvir (SOF) is a nucleotide analog inhibitor of viral NS5B polymerase, the key enzyme mediating HCV-RNA replication. The triphosphate form of SOF mimics the natural cellular uridine nucleotide and is incorporated by the HCV RNA-polymerase into the elongating RNA primer strand, resulting in chain termination. In the "Valence" study the combination of SOF and RBV (12 wk) demonstrated 93% SVR in genotype 2 patients, while in genotype 3 patients the same combination administered for 24 wk obtained 85% SVR[53]. Ledipasvir (LDV) is a potent inhibitor of HCV NS5A, a viral phosphoprotein that plays an important role in viral replication, assembly, and secretion. The combination of LDV (90 mg) and SOF (400 mg) at fixed-dose combination (FDC) has been primarily studied as an all-oral IFN-free combination regimen in treatment-naïve and treatment-experienced patients as the first once-daily single tablet regimen to treat the majority of chronic HCV genotype 1 and 4 infection. LDV-SOF FDC obtained 99% SVR in genotype 1 treatment-naïve patients in "ION-1 study"[54], and 95% in genotype 4 patients in "NIH Synergy study"[55]. Moreover, preliminary data of *Electron-2 study* demonstrated that the combination of LDV-SOF and RBV administered for 12 wk induced 100% SVR in genotype 3 patients[52]. Finally, the recently reported "ASTRAL studies" pointed out the impressive results of the combination of SOF with the new pangenotypic NS5A inhibitor Velpatasvir, which demonstrated SVR of 97%-100% across all 6 genotypes and resulted superior to SOF-RBV in genotype 2 (SVR 99% *vs* 94%) and 3 (SVR 95% *vs* 80%) in a randomized comparison.

Preliminary data about interferon-free antiviral treatment in HCV-associated indolent lymphomas

As previously discussed, the lymphoma regression observed in nearly 75% of patients with IFN-based AT, which has been closely associated with HCV eradication, is strongly in favor of a causative role of HCV in a subset of patients with indolent NHL, although the direct anti-lymphoma properties of IFN cannot be ruled out. For this reason, the introduction in HCV-associated NHL therapy of the highly active DAA-based IFN-free regimens, that demonstrated SVR rates ⩾ 90% also in genotype 1, is expected to definitely clarify this point. To date, six cases of HCV-positive NHL treatment with DAA IFN-free regimen have been reported, three in SMZL, two in MALT-type MZL and one in leukemic MZL[58-61]. In all these cases the SVR obtained with various DAA IFN-free regimens (manly SOF-based) has been followed by partial or complete hematologic response (Table 2).

In details, in the first one case report by Italy, a 42-year old patient carrying genotype 1 HCV infection and SMZL with lymphocytosis has been treated with a 16 wk regimen of Faldaprevir (NS3/NS4 protease inhibitor), Deleobuvir (non-nucleoside NS5B inhibitor) and RBV. This DAA combination led to a RVR (HCV-RNA undetectable after 4 wk) and to a concurrent resolution of splenomegaly and lymphocytosis[58]. In the second case report from France a 57-year old female with genotype 3a HCV infection and stage Ⅳ disseminated MALT-type MZL (breast, humeral shaft and cervical lymph node involvement) has been treated for 4 wk with SOF and RBV and then, after obtainment of HCV-RNA clearance, with a 12-wk regimen with SOF and Daclatasvir (NS5A inhibitor). After 12 wk a SVR was confirmed (SVR12) and a CT scan showed a complete regression of lymphoma localizations (CR), which was still ongoing at the time of publication after 6 mo of follow-up[59]. Three other cases were described by another French paper focusing on the use of DAA in patients with lymphomas. The first patient was a 54-years old female with a history of previous intravenous drug abuse chronically infected with genotype 4 HCV. After diagnosis of a leukemic MZL (6000/mmc clonal B-cells in peripheral blood) with mixed cryoglobulinemia (cryocrit 5%), she underwent to AT with 12-wk of SOF and Simeprevir (NS3/NS4

Table 2 Direct-acting antiviral agents-based antiviral treatment in hepatitis C virus-infected patients with low-grade non-Hodgkin lymphomas

	Year	No. of patients	Diagnosis	Genotypes	Cryoglobulinemia	Antiviral treatment	Virologic response	NHL response
Rossotti *et al*[58]	2015	1	SMZL	1b	Yes (type Ⅱ MC)	FDV + DLV + RBV (16 w)	SVR	PR
Sultanik *et al*[59]	2015	1	MALT MZL (breast, humeral shaft, cervical lymph node)	3a	Yes (type Ⅱ MC)	SOF + RBV (4 w), then SOF + DCV (12 w)	SVR	CR (ongoing at 6 m)
Carrier *et al*[60]	2015	3	1 Leukemic MZL	4	3 (type Ⅱ MC)	SOF - SIM	3 SVR	PR
			1 MALT MZL (kidney)	1b		SOF - SIM + 4 Rtx		CR
			1 SMZL	1b		SOF - DCV		CR
Lim *et al*[61]	2015	1	SMZL	2	No	SOF + RBV (12 w)	SVR	CR (ongoing at 17 m)
Arcaini *et al*[62]	2015	20	9 SMZL	1 (n = 13)	10 (50%)	various	19 SVR	4 CR, 2 PR, 2 SD 1 PD
			1 NMZL (Nodal)	2 (n = 3)		SOF-based regimens		1 CR
			5 MALT MZL	3 (n = 3)				2 CR, 1 PR, 2 PD
			2 Leukemic MZL	4 (n = 1)		(+ 4 Rtx in 1 pts)		1 CR, 1 PR
			2 CLL					2 SD
			1 LPL					1 SD

DAA: Direct-acting antiviral agents; SMZL: Splenic marginal zone lymphoma; NMZL: Nodal marginal zone lymphoma; phocytes; MZL: Marginal zone lymphoma; LPL: Lymphoplasmacytic lymphoma; MC: Mixed cryoglobulinemia; FDV: Faldaprevir; DLV: Deleobuvir; RBV: Ribavirine; SOF: Sofosbuvir; DCV: Daclatasvir; SVR: Sustained virologic response; CR: Complete response; PR: Partial response; SD: Stable disease; PD: Progressive disease; Rtx: Rituximab.

protease inhibitor), obtaining SVR12 together with partial hematologic response (1000/mmc clonal B-cells in peripheral blood) and clearance of cryoglobulins. The second patient (66-year old male) carrying genotype 1b and presenting with compensated cirrhosis (Child score 5) was diagnosed with stage Ⅳ SMZL with associated type Ⅱ mixed cryoglobulinemia (cryocrit 79%). He was treated with 24 wk combination of SOF and Daclatasvir, obtaining SVR12, haematological CR and reduction of circulating cryoglobulins (cryocrit 9%). Unfortunately he developed thereafter a metastatic hepatocellular carcinoma. The third patient (66 years-old female, genotype 1b) presented with rapidly progressive chronic renal insufficiency and 7% circulating cryoglobulins. A renal biopsy showed monomorphous small B-cell infiltrate and diagnosis of renal MALT-MZL was made. Due to the pre-dialisis life-threatening renal failure she was treated with 4 weekly doses of rituximab plus AT with SOF and Simeprevir for 12 wk, that enabled to obtain together with SVR12 a significant improvement of glomerular filtrate and the disappearance of MZL infiltrate at the control kidney biopsy (haematological CR), although a residual weak B-cell clonality (by study of immunoglobulin genes rearrangement) was still detectable[60]. The last published case report from Canada described a 70-year-old woman presenting with severe thrombocytopenia. Routine serology discovered a previously unrecognized genotype 2 HCV infection with high titer HCV-RNA. Peripheral blood and bone marrow testing revealed an aberrant monoclonal B-cell population (CD20-positive), although no splenomegaly or adenopaties were evident. After failure to a variety of immune-suppressive therapies for thrombocytopenia she underwent splenectomy and SMZL diagnosis was made. She was then treated with SOF and RBV for 12 wk resulting in RVR, resolution of thrombocytopenia and flow-cytometry negativity for residual clonal B-cells (CR), remaining ongoing at more than 18 mo of follow-up[61].

At the last ASH meeting (2015), Arcaini *et al*[62] presented preliminary data of a large international survey on 26 patients with indolent lymphoproliferative disorders (12 SMZL, 2 NMZL, 6 MALT-MZL, 2 leukemic MZL, 2 SLL/CLL, 1 LPL and 1 low grade B-NHL NOS) and HCV infection treated with IFN-free AT. Three patients previously received chemotherapy and 4 a course of IFN-based AT. HCV genotype was 1 in 63%, 2 in 17% and 3 in 12% of patients. The majority of patients (n = 24) received a SOF-based regimen and 2 other regimens. A RVR was obtained in 20 out of 21 evaluable patients (95%). Considering 20 patients evaluable for lymphoma response, 8 achieved a CR (40%), 4 a PR (20%), with an ORR of 60%, while 5 had SD and 3 progressed during AT. According to histological subtypes, ORR was 70% in MZL (12 out of 17 patients), including 6 out of 9 SMZL (66%), while none of the 3 patients with other subtypes responded (2 CLL and 1 LPL, all SD). In conclusion this preliminary study showed that a significant rate of hematological response can be achieved in HCV-associated MZL also with DAAs, thus suggesting that the eradication of HCV may be able *per se* to induce the regression of indolent NHLs. Although these data have to be confirmed by larger series with longer follow-up, MZL seem to be more sensible to IFN-free AT, while subtypes less clearly associated with HCV such as CLL probably are not responsible to it.

On the basis of these preliminary data, the FIL initiated the phase Ⅱ BArT study (B-cell Anti-lymphoma Treatment), the first prospective clinical trial aimed to evaluate the efficacy, both virological and

haematological, of an IFN-free antiviral regimen in patient with indolent NHL associated with HCV infection. In this multicenter study, 50 patients with genotype 1-4 chronically active (HCV-RNA positive) non-cirrhotic HCV infection and untreated indolent asymptomatic NHL (with low tumor burden) will receive appropriate IFN-free AT according to genotype.

CONCLUSION

A large body of studies carried out in the last decade demonstrated that front-line IFN-based anti-HCV AT is able to induce nearly 75% response rate in all HCV-associated indolent B-cell lymphomas that do not need immediate conventional immuno-chemotherapy. Moreover, AT delivered at any time during patients' life has been associated with significantly improved OS. As in IFN era lymphoma response has been durable and related to the obtainment of viral eradication. Very preliminary data about the use of DAAs as primary treatment of indolent NHL seem to confirm that together with high rate of SVR in all genotypes they are able to induce a proportion of tumor responses, despite the absence of IFN therapy. More mature data of retrospective experiences as well as ongoing prospective studies are needed to precisely clarify their impact in HCV-positive B-NHL. Moreover, a promising area of future investigation may deal with the combination of DAA and rituximab, especially in cases with high tumor-burden. Because of its safety, rapidity and efficacy, AT should be recommended front line to patients with HCV-positive indolent NHL, both for the expected curative activity on the tumor itself, and because eradicating HCV is *per se* beneficial to the patient, avoiding late complications of the infection and allowing better tolerability to eventual future conventional anti-lymphoma treatments.

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