INTERFERON-FREE ANTIVIRAL TREATMENT IN B-CELL LYMPHOPROLIFERATIVE DISORDERS ASSOCIATED WITH HEPATITIS C VIRUS INFECTION

Running title: DAAs in HCV-associated lymphomas

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**Key points:**
- Direct-acting antivirals agents are able to induce lymphoma response in patients with HCV-associated indolent non-Hodgkin lymphoma.
- The highest rate of lymphoma response (73%) was observed in patients with marginal zone lymphoma.
Regression of hepatitis C virus (HCV)-associated lymphoma with interferon-based antiviral treatment supports an etiological link between lymphoma and HCV infection. In addition, a favorable impact of antiviral treatment on overall survival of patients with HCV-related lymphoma has been reported. Data on IFN-free regimens combining direct-acting antivirals (DAAs) in HCV-associated lymphoproliferative disorders are scanty.

We analyzed virological and lymphoproliferative disease response (LDR) of 46 patients with indolent B-cell non-Hodgkin lymphomas (NHL) or chronic lymphocytic leukemia (CLL) and chronic HCV infection treated with DAAs.

Histological distribution was: 37 marginal zone lymphomas (MZL), 2 lymphoplasmacytic lymphomas, 2 follicular lymphomas, 4 CLL/small lymphocytic lymphoma (SLL), 1 low-grade NHL not otherwise specified. Thirty-nine patients received a Sofosbuvir-based regimen and 7 patients other DAAs. Median duration of DAA therapy was 12 weeks (range 6-24 weeks). A sustained virological response at week 12 after finishing DAAs was obtained in 45 patients (98%); overall LDR rate was 67% including 12 patients (26%) achieving a complete response. LDR rate was 73% among patients with MZL while no response was observed in CLL/SLL patients. Seven patients cleared cryoglobulins out of 15 initially positive. After a median follow up of 8 months, 1-year progression-free and overall survival were 75% [95% confidence interval: 51% - 88%] and 98% [86-100%], respectively.

DAA therapy induces a high LDR rate in HCV-associated indolent lymphomas. These data provide a strong rationale for prospective trials with DAAs in this setting.
INTRODUCTION
In addition to liver disease, hepatitis C virus (HCV) infection has been linked to the development of type II mixed cryoglobulinemia and to a spectrum of B-cell lymphoproliferative disorders. Systematic reviews of epidemiological studies evaluating the prevalence of HCV infection in B-cell non-Hodgkin lymphomas (B-NHL) confirmed that HCV prevalence is higher in patients with B-NHL than in general population, supporting a role of HCV in the etiology of B-NHL. In subtype-specific analysis, HCV infection is associated with marginal zone lymphoma (MZL), diffuse large B-cell lymphoma (DLBCL) and lymphoplasmacytic lymphoma (LPL). The pathophysiology of HCV-associated B-NHL, at least for MZL, appears to be linked to chronic antigenic stimulation, as several reports show that the clearance of HCV infection with interferon (IFN)-based antiviral therapy often results in regression of the tumor burden. The favorable impact of IFN-based antiviral therapy on the outcome of these patients has been consistently reported in the Fondazione Italiana Linfomi study and in the French ANRS HC-13 Lympho-C study. However, a direct anti-proliferative effect of IFN on malignant lymphocytes cannot be ruled out.

The therapy of HCV infection is undergoing a transformation. After nearly 25 years of IFN-based therapies, a new era for direct-acting antiviral (DAA) drugs has entered clinical practice. Recently, several DAAs were approved as part of different IFN-free combination therapies. These include second-generation NS3/4A inhibitors (simeprevir, ritonavir-boosted paritaprevir, grazoprevir), NS5A inhibitors (daclatasvir, ledipasvir, ombitasvir, elbasvir), a nucleotide polymerase inhibitor (sofosbuvir), and a non-nucleoside polymerase inhibitor (dasabuvir). In term of efficacy, DAA therapy can induce viral eradication in >90% of all patients across different genotypes and fibrosis stages with the exception of some patient subgroups (e.g. patients with decompensated cirrhosis). Furthermore, DAAs regimens are associated with a better safety and tolerability profile than IFN treatment and thus may represent an attractive alternative to manage HCV-associated NHL simultaneously.

However, data on the efficacy of IFN-free regimens in HCV-associated lymphoproliferative disorders are scanty and based on clinical reports. In this study we have evaluated virologic and lymphoproliferative disease response (LDR) rates and toxicity of DAAs in a large series of patients with indolent lymphoproliferative disorders treated by DAAs in the absence of immunochemotherapy.
METHODS

Study design and patients
We retrospectively selected patients affected by indolent B-NHL or chronic lymphocytic leukemia (CLL) and infected by HCV defined as HCV-RNA positivity and treated with DAAs within Italian centers of Fondazione Italiana Linfomi, the French ANRS-CO22 HEPATHER cohort, in a German center (Frankfurt) and in a United States center (Houston). Five patients were already reported in the literature\textsuperscript{10-12} and were included with updated follow-up. Approval for this study, which was based on the use of archival or cohort data, was obtained from the Institutional Review Boards of participating centers. The report was prepared in accordance with the STROBE statement.\textsuperscript{13} Data management and analysis were carried out in accordance with the tenets of the Declaration of Helsinki of 1964, as revised in 2000. All patients gave informed consent.

Clinical and virological end-points
The primary end-point was overall response rate (ORR); complete response (CR), partial response (PR) rates, progression-free survival (PFS) and overall survival (OS) were secondary end-points. PFS was defined as the time interval between the start of DAA therapy and lymphoma progression, initiation of new treatment, or death. Response evaluation was based on Lugano classification criteria for lymphomas\textsuperscript{14} and on guidelines from the International Workshop on CLL.\textsuperscript{15} Specific examinations were carried out for response assessment in specific lymphoma subtypes, according to clinical presentation (i.e. paraprotein level when present before DAA). Bone marrow biopsy was repeated at the end of DAA only in cases that were positive at study entry. Response assessment was performed one month after the end of DAA therapy. Sustained virological response (SVR) was defined as undetectable HCV viral load (<15 IU/ml) 12 weeks after completion of therapy.
Statistical analysis
The Fisher's exact test was used to explore associations between categorical variables. The Wilcoxon rank-sum test was applied to test differences of quantitative variables between two independent groups. The associations between clinical variables and non-response were reported in terms of Odds Ratio (OR), 95% confidence interval (95% CI) and significance level (p-value). All variables with a p-value ≤0.1 in the univariate analysis of non-response were included in a multivariate logistic model. The Kaplan–Meier product-limit method was used to estimate PFS and OS. All computations were carried out using Stata 12.1 (2007).

RESULTS
Hematological and virological features
Hematological and virological characteristics of the 46 study patients are summarized in Table 1. There was a slight female predominance (61%) and median age was 59 years. Only three patients had CLL while the other 43 patients had NHL. The main histological NHL type was MZL (37 patients, 81%) among which 15 were extranodal MZL of MALT (all extragastric and 3 with multiple MALT site). Among all NHL patients, predominantly involved sites were spleen (n=22) and liver (n=6). Serum monoclonal component was present in 19 patients and cryoglobulins were detectable in 15 patients among which 6 were symptomatic. Seven patients were cirrhotic (5 Child-Pugh A, 2 Child-Pugh C). No patient was co-infected with HIV and one patient had concomitant hepatitis B virus infection (HBV surface antigen positive). Ten patients had previously received chemotherapy and 12 an IFN-based antiviral regimen. Treatment was a sofosbuvir (SOF)-based regimen in all but 7 patients. Median duration of treatment was 12 weeks (range 6-24 weeks). In one patient with renal MZL, 4 weekly Rituximab doses were added to DAA. All patients, except one who received only 6 weeks of DAA therapy for early progression, were treated with the whole course of DAA therapy.

Toxicity
Toxicity of treatment was negligible: 13 patients had grade 1-2 adverse events (including five cases of anemia in patients treated with ribavirin) and only one grade 3 event was registered (asthenia).

Virological response and lymphoproliferative disease response
DAA treatment led to a virological response in all patients except one who had decompensated cirrhosis. Hematological ORR was 67%, CR being obtained in 12 cases
(26%), and PR in 19 (41%). Eleven patients had stable disease (24%) and four early progressed. LDR rate was 73% in patients with virological response and absent in the single case without virological response. Responses according to histological subtypes are summarized in Table 2. ORR was 73% in MZL (27/37) and 44% in non-MZL lymphoproliferative disorders (4/9). Remarkably, none of the 4 CLL/SLL cases exhibited responses. Among 7 cirrhotic patients, one obtained a CR, one a PR, 4 a SD, 2 a progression while 6 had a virological response. Finally, seven patients out of 15 initially positive, cleared cryoglobulins.

Since no LDR was observed among the CLL/SLL patients, we analyzed the predictive factors of LDR within the 42 cases of NHL only. In univariate analysis, there was a trend toward a higher risk of non-response in patients with nodal disease and in patients with low hemoglobin levels. On the contrary, patients with extranodal disease and patients with serum monoclonal component have shown a trend to a lower risk of non-response (p-values<0.1) (Supplemental table 1). In multivariate analysis risk of non-response was significantly lower in pts with serum monoclonal component respect to pts without component (OR=0.1; 95%CI: 0.1-1.0; p=0.048). Furthermore, presence of extranodal disease showed a trend toward a lower risk of non-response (OR=0.1; 95%CI: 0.1-1.1; p=0.059). On the contrary, no effect was found for the presence of nodal disease (OR=6.5; 95%CI: 0.5-81.9; p=0.150) and for low hemoglobin level (OR=2.4; 95%CI: 0.4-16.4; p=0.357).

**Outcome**

After a median follow up since start of DAA therapy of 8 months (range: 2 - 30), median PFS is not reached and estimated 1-year PFS is 75% [95%CI: 51% - 88%] (Figure 1). Median OS is not reached and estimated 1-year OS is 98% [86 % - 100 %] (Figure 2). Four early progressions occurred during (n=1) or within 3 months after the end of DAA therapy (n=3). The first patient was treated with DAA because of Child C cirrhosis with encephalopathy and a concomitant extranodal MZL with high tumor burden; he had no virological or lymphoma response and died 4 weeks after the early interruption of DAA therapy. Another extranodal MZL patient relapsed soon after the interruption of DAA and received immunochemotherapy that led to CR. One patient with SMZL, despite a rapid virological response, developed a rapidly growing kidney mass that was diagnosed as transformed DLBCL. One patient with a previous diagnosis of extranodal MZL had an early progression after DAA therapy and is now under chemotherapy treatment.

Two patients with SMZL progressed more than 3 months after the end of DAA therapy. One was treated with immunochemotherapy resulting in PR. One patient progressed 6 months
after the end of DAA therapy with worsening cytopenias but is still in observation. Lastly, a patient with SMZL died of hepatocellular carcinoma 8 months after the end of DAA therapy while in hematological PR (8 months after the end of DAA therapy).
DISCUSSION

Here, we report the first large series of patients with HCV-associated lymphoproliferative disorders treated with IFN-free DAA therapy. As described in HCV infection without lymphoma\textsuperscript{16}, this study confirms that virological response is obtained in nearly all patients with chronic HCV infection (98%). This high rate of virological response was associated to an overall LDR rate of 67% including complete and partial responses in 26% and in 41% of patients, respectively.

Epidemiological studies provide strong evidences for an association of HCV infection with B-cell lymphoproliferative disorders, in particular with the histological subtypes MZL\textsuperscript{17} and DLBCL.\textsuperscript{18,19} The most convincing evidence for a causal relationship between HCV infection and lymphoma development is the observation of lymphoma regression after HCV eradication by antiviral therapy.\textsuperscript{4-6,20} In a recent meta-analysis of 20 studies (254 patients) evaluating the efficacy of IFN-based treatment in HCV-related NHL, overall lymphoma response rate after IFN-based antiviral therapy was 73% which is similar to the ORR reported in the present study.\textsuperscript{21} In studies using IFN-based antivirals in which rate of virological response was lower, a strong correlation between virus clearance and lymphoma response has been established. In the present study, the only patient who did not achieve SVR at week 12 to DAA also underwent lymphoma progression leading to early death.

Regarding the association between histological type and lymphoma response, in the above cited metanalysis\textsuperscript{21}, there was a trend towards favorable response for antivirals in HCV-associated MZL (response rate 81%), compared to non-marginal zone lymphomas (response rate 71%). The higher lymphoma response rate in MZL is confirmed in our series: ORR is 73% for MZL and 44% for non-MZL. Of note, MZL subtype exhibits similar response rates than those obtained with IFN-based regimen. Taking into account the relatively low number of cases, we found trends for a better lymphoma response in patients with extranodal disease and paraproteinemia, features typically associated with HCV-associated NHLs.\textsuperscript{22-24} Finally, in CLL/SLL, that are not constantly epidemiologically associated with HCV infection\textsuperscript{3,25}, no LDR were achieved despite virus clearance. Altogether, these findings confirm that HCV clearance per se is beneficial in patients with non CLL/SLL HCV-associated B-NHL and support a stepwise model of lymphomagenesis induced by chronic antigenic stimulation in this setting.

Taken together, considering the favorable impact of IFN-based antivirals on outcome of HCV-infected NHL patients,\textsuperscript{5,6} our data strongly suggest that antiviral treatment should be used as the first option for HCV-associated MZL when cytoreductive treatment is not immediately necessary.\textsuperscript{26-28} An extended follow up of this series will be necessary to confirm
that responses are sustainable even in the group of patients in PR as long as virological response was maintained, suggesting that hematological CR is not a mandatory therapeutic goal to reach in this setting. Although follow-up is still short, especially for a series of indolent lymphomas, the rapid lymphoma and virological responses along with the good safety profile that we describe suggest that DAA therapy should be used in first line in patients with HCV-associated MZL, also with absent or mild liver impairment. Consistently with this recommendation, Torres et al. recently demonstrated that the majority of patients with HCV-NHL have low liver fibrosis at NHL diagnosis.29 Our data also support the use of DAA in patients with indolent lymphoma in progression or relapse after previously treatment with immunochemotherapy. On the other hand, combination of Rituximab and IFN-based antivirals proved to be feasible and efficient in patients with cryoglobulinemia and lymphoproliferative B-cell disorders.30,31 Further studies are warranted to evaluate the place of this combination in the treatment of patients with advanced, rapidly progressive and/or symptomatic disease. Limits of this retrospective study are heterogeneity of antiviral treatments, variable length of follow-up, possible selection bias, and limited length of follow-up. In particular, due to the retrospective nature of this analysis, criteria for initiating treatment are probably heterogeneous.

In conclusion, HCV infected patients with indolent B-NHL, especially of marginal zone origin, benefit from antiviral therapy. Because of DAA safety, rapidity and efficacy to obtain virological response as well as good tolerance profile, DAA therapy should be preferred to IFN-based antiviral treatment. It can be proposed in first line and in patients in progression or relapse with no need for immediate immunochemotherapy. These results provide a strong rational background for larger prospective series to determine precisely the impact of DAA therapy in HCV-infected patients with B-cell NHL.
Author contributions: L.Ar., C.B., C.V., O.H. designed and supervised the overall conduction of the study; V.V.F., L.Ar., M.F. and C.V. analyzed the data; L.Ar. wrote the manuscript; L.A. and C.V. collected the data; L.Ar., C.B., M.F., M.G., M.C., M.V., H.A.T., V.L.R., J.P.O., P.F., R.R., F.Z., L.R., S.R., R.B., M.M., H.F., L.Al., C.D., S.P., F.C., C.V. and O.H. enrolled and cared for the patients; L.Ar., C.B., C.V. and O.H. reviewed the manuscript and all authors approved the final manuscript.

Conflict-of-interest disclosure: L.Ar. received advisory honoraria from Bayer, Celgene, Gilead, Roche and Sandoz and research support from Gilead. H.A.T is or has been the principal investigator for research grants from Gilead Sciences, Merck & Co., Inc., and Vertex Pharmaceuticals, with all funds paid to MD Anderson. H.A.T also is or has been a paid scientific advisor for Gilead Sciences, Janssen Pharmaceuticals, Inc., Merck & Co., Inc., Vertex Pharmaceuticals, Genentech, Novartis, Astellas Pharma, Pfizer Inc., and Theravance Biopharma, Inc.; the terms of these arrangements are being managed by MD Anderson in accordance with its conflict of interest policies. V.L.R. received advisory honoraria from BMS, Gilead, Abbvie, MSD and research support from BMS and Roche; R.B. received advisory and/or lecture honoraria from Abbvie, BMS, Gilead, MSD and Janssen.

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FIGURE LEGENDS

Figure 1. Progression-free survival of 46 patients with B-cell lymphoproliferative disorders associated with hepatitis C virus infection treated with direct-acting antiviral agents

Figure 2. Overall survival of 46 patients with B-cell lymphoproliferative disorders associated with hepatitis C virus infection treated with direct-acting antiviral agents
Table 1. Features of the 46 patients with B-cell lymphoproliferative disorders associated with HCV infection treated with direct-acting antivirals

<table>
<thead>
<tr>
<th>Category</th>
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<th>%</th>
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<tbody>
<tr>
<td>Age (years), median (range)</td>
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<td>-</td>
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<td>Male/female</td>
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<td>- Marginal zone lymphomas</td>
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</tr>
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<td>- Nodal</td>
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<tr>
<td>- Extranodal</td>
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<td>32</td>
</tr>
<tr>
<td>- Leukemic</td>
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<td>9</td>
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<tr>
<td>- Others*</td>
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<td>- CLL/SLL</td>
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*: follicular lymphoma (n=2); lymphoplasmacytic lymphoma (n=2); low-grade B-cell NHL non otherwise specified (n=1).

**: sofosbuvir combined with simeprevir (n=13), ribavirin (n=15), daclatasvir (n=8), ledipasvir (n=3).

**: paritaprevir/ritonavir/ombitasvir +/- dasabuvir +/- ribavirin (n=6), faldaprevir/deleobuvir/ribavirin (n=1)
Table 2. Lymphoproliferative disease response to direct-acting antivirals according to histological subtypes in 46 patients with B-cell lymphoproliferative disorders associated with hepatitis C virus infection

<table>
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<th>Subtype</th>
<th>Complete Response (n)</th>
<th>Partial Response (n)</th>
<th>Stable Disease (n)</th>
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<td>All (n=46)</td>
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NHL: non-Hodgkin lymphoma; NOS: not otherwise specified; CLL: chronic lymphocytic leukemia; SLL: small lymphocytic lymphoma

*: follicular lymphoma (n=2); lymphoplasmacytic lymphoma (n=2); low-grade B-cell non-Hodgkin lymphoma not otherwise specified (n=1).
Figure 1

Cumulative proportion surviving vs. Time (months)

Number at risk: 46
Interferon-free antiviral treatment in B-cell lymphoproliferative disorders associated with hepatitis C virus infection

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