The association between the hepatitis C virus and B-cell non-Hodgkin’s lymphomas is controversial. We review the epidemiological evidence behind the association, and look at the reasons behind the variation in study findings. There is increasing evidence of the pathogenesis of hepatitis C-associated lymphoma. Treatment of the hepatitis C virus with antiviral therapy may lead to the regression of some low-grade lymphomas. The management of other hepatitis C-associated lymphomas is similar to that of conventional lymphoma, although viral reactivation and subsequent immune reconstitution hepatitis can complicate chemotherapy.

**Key words:** hepatitis C, lymphoma, pathogenesis

**Introduction**

The number of viruses associated with lymphoma has increased over the last 20 years, and includes the Epstein–Barr virus (EBV), human T-cell lymphotropic virus 1 (HTLV1), human immunodeficiency virus (HIV1 and 2) and human herpesvirus 8 (HHV8). Some cause lymphoma by direct oncogenesis, for example EBV and Burkitt’s lymphoma. Others cause lymphoma in immunosuppressed patients, for example HHV8 in primary effusion lymphoma and Castleman’s syndrome. Lymphomas in HIV patients arise directly due to HIV action on lymphocytes and secondary to AIDS, with up to 50% of these lymphomas associated with EBV. Successful treatment of virus-associated lymphomas is often difficult, either due to their aggressive behaviour, for example Burkitt’s lymphoma, or due to the inadequate dose intensity or development of infection associated with chemotherapy in patients who are already immunosuppressed.

Hepatitis C virus (HCV) has only recently been recognized as a potential cause of B-cell lymphoma. The management of these lymphomas is also complicated by the presence of the underlying chronic HCV infection [1, 2]. We discuss the available evidence on the epidemiology of HCV and lymphoma, recent insights into the pathogenesis, and the management of HCV during treatment.

**Hepatitis C and lymphoma: a controversial association?**

The potential association of HCV and non-Hodgkin’s lymphomas (NHL) was first recognized while studying patients with essential mixed cryoglobulinaemia (EMC), a chronic autoimmune disease with an underlying bone marrow B-cell clonal proliferation [3]. Chronic hepatitis C infection was recognized as the principle cause of EMC 10 years ago, with antibodies to the virus found in 84–98% [4, 5] of patients with EMC. EMC predisposed to development of malignant lymphoma [6], prompting further studies on the association between hepatitis C and lymphomas.

**Studies with a positive association**

The epidemiological data supporting a general association of HCV and lymphoma remains controversial, with considerable discordance between reports. The majority of positive studies have originated in Italy, where the prevalence of HCV is particularly high, with reported prevalences of up to 2.9% in parts of the north of the country [7], and up to 12.6% in parts of the south [8]. The lymphoma with the clearest link to HCV is lymphoplasmacytoid lymphoma, an overt B-cell lymphoma that can complicate EMC, with up to 30% of cases associated with hepatitis C [9, 10]. These initial studies compared the rate of HCV antibodies in retrospective cohorts of lymphoma patients with the healthy background population as control. It was not until larger case–control studies were performed that a more general association with other B-cell malignancies was found.

There has been a recent proliferation of papers on the association between HCV and NHL. A general association of HCV and B-cell NHL has been reported in studies from Brazil [11], Italy [12–15], Israel [16], Japan [17, 18], Romania [19], Turkey [20], Switzerland [21] and the USA [22]. Some of these studies have used inappropriate control groups, such as healthy blood donors, which potentially confound interpretation, and those studies are not discussed here. Studies that have used more appropriate control groups, including those from Italy [13–15], Japan [18] and the USA [22], have found a general association of B-cell NHL and chronic infection with HCV (Table 1). A further paper from Italy has produced equivocal results (Table 1) [23].

Both Hodgkin’s lymphoma and T-cell NHL consistently show no association with HCV. There may be an association of myeloma with HCV, in addition to B-cell lymphomas (Table 1). Although initial studies on HCV associations focused on lymphocytolys-
studies have failed to find an association? Clearly one possible evidence of a significant association [36]. Why might these association discussed above, a further Japanese study found little association. In contrast to the Japanese studies supporting the [32], Turkey [33], Thailand [34] and the USA [35] failing to find small negative series from the UK [29], Canada [30, 31], Germany a recent large case.

The finding of an association is not universal in the literature, with Studies showing no association

The finding of an association is not universal in the literature, with a recent large case–control study from France [28], and multiple small negative series from the UK [29], Canada [30, 31], Germany [32], Turkey [33], Thailand [34] and the USA [35] failing to find an association. In contrast to the Japanese studies supporting the association discussed above, a further Japanese study found little evidence of a significant association [36]. Why might these studies have failed to find an association? Clearly one possible interpretation would be that there is no association between lymphoma and HCV. Many positive studies are well conducted, however, and other reasons are likely to explain the discrepancies between studies. At best, only a small minority of HCV carriers will develop lymphoma, otherwise countries with a high prevalence of HCV carriage would be overwhelmed by cases of lymphoma. An accurate assessment of the exact risk could only come from a large cohort study, and no such studies have been reported. Many of the negative studies have been small, and hence lacking adequate power, or have studied populations with a low prevalence of HCV carriage, and hence have only been able to identify a weak association [28]. It is also possible that there may be a geographical variation in the association, with cofactors such as geographical differences in viral genotype, population genetics or environmental factors underlying the differences between studies. There is, however, no direct evidence to support or refute these possibilities. From the available evidence it appears that HCV is only an important risk factor for B-cell malignancies in areas with a high prevalence of HCV carriage.

Potential mechanisms of pathogenesis of hepatitis C-associated lymphoma

HCV is a member of the RNA flavivirus family. The virus lacks reverse transcriptase, and hence is unable to integrate into the host genome and does not encode for any known oncogenes. The pathogenesis of hepatocellular carcinoma associated with HCV has been much studied, but still remains largely unknown. There is increasing evidence that HCV-encoded proteins may contribute to the pathogenesis of hepatocellular carcinoma. HCV proteins

<table>
<thead>
<tr>
<th>Study</th>
<th>HCV infection rates in B-cell disorders</th>
<th>HCV infection rates in controls</th>
<th>Odds ratio (95% CI) for HCV infection</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Rosa et al. [14], Italy</td>
<td>B-cell lymphoproliferative disorders: 59/263 (22.4%)</td>
<td>T-cell NHL or Hodgkin’s lymphoma: 1/52 (1.9%)</td>
<td>0.0016</td>
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<tr>
<td>Zuckerman et al. [22], USA (78% Hispanic)</td>
<td>B-cell NHL: 26/120 (22%)</td>
<td>Other malignant haematological conditions: 7/154 (4.5%)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Montella et al. [13], Italy</td>
<td>High-grade B-cell NHL: 10/22 (48%)</td>
<td>Hodgkin’s lymphoma: 5/63 (8%)</td>
<td>11.5 (4.2–32.2)</td>
<td>&lt;0.0001</td>
</tr>
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<td></td>
<td>Intermediate-grade B-cell NHL: 11/48 (23%)</td>
<td>General medical admissions: 17/225 (8%)</td>
<td>3.2 (1.3–7.5)</td>
<td>0.006</td>
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<td></td>
<td>Low-grade B-cell NHL: 3/31 (10%)</td>
<td></td>
<td>1.1 (0.3–4.3)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Multiple myeloma: 13/41 (32%)</td>
<td></td>
<td>4.5 (1.9–10.7)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Vallisa et al. [15], Italy</td>
<td>NHL: 65/175 (37%)</td>
<td>‘Selected inpatients and outpatient’: 27/300 (9%)</td>
<td></td>
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<tr>
<td>Mizorogi et al. [18], Japan</td>
<td>B-cell NHL: 17/100 (17%)</td>
<td>Non B-cell NHL: 0/25 (0%)</td>
<td>0.023</td>
<td></td>
</tr>
<tr>
<td>Piotelli et al. [23], Italy</td>
<td>B-cell NHL: 48/300 (16%)</td>
<td>Age-/sex-matched controls: 51/600 (8.5%)</td>
<td>2.0 (0.7–27)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CI, confidence interval; NHL, non-Hodgkin’s lymphoma; NS, not significant.

Table 1. Selected case–control studies demonstrating the association of HCV infection with B-cell NHL and B-cell lymphoproliferative disorders

Chronic infection with HCV indicated by the presence of HCV antibodies, and confirmed by HCV RNA detection by RT–PCR in references [13–15, 22; 23].

MACROCYTIC LYMATHOMA

Macrophagolymphoid hyperplasia, also known as lymphoplasmacytoid lymphoma as the principal HCV-associated lymphoma [9, 10], this lymphoma is not prominent in many later series. In some series, low grade histologies predominate [12, 14, 21], but in other series the association is with intermediate- or high-grade lymphomas [13, 16, 18]. It is unclear if this simply represents ascertainment bias, reflecting local referral practices and different case mixes, or is a more significant finding.

The presentation of NHL associated with HCV differs from standard NHL. Lymphomas associated with HCV more commonly present as primary extra-nodal lymphomas, especially liver, spleen and salivary glands [13, 24, 25]. Indeed, as many as 65% of diffuse large B-cell lymphomas associated with HCV may present as primary extra-nodal lymphomas, compared with 19% of controls [24]. This mirrors the ability of the hepatitis virus to infect these organs [26]. Cryoglobulinaemia is more frequently found in HCV-associated lymphomas, especially lymphomatosclerotic lymphoma [10]. Retrospective studies of patients whose infection date can be accurately determined, suggest the mean latency from acquiring the virus to presentation with lymphoma is 15 years [22, 27].
can interfere with signal transduction, growth regulation and apoptosis. HCV proteins, for example the Core protein, have the ability to transform mouse fibroblast cells in vitro [37], and transgenic mice expressing HCV core proteins have, in some studies, developed liver tumours.

HCV infection becomes chronic in up to 86% of cases of seroconversion [38]. Although the virus excites an active immune response, the virus evades the immune system by unknown mechanisms. Possible methods of evasion include escape mutations in HCV genes [39], defects in antigen recognition, and in addition the virus can infect B lymphocytes, which act as a sanctuary site protected from immune attack by T cells [40].

There is evidence that HCV can induce clonal proliferation of B-cells in patients carrying the virus chronically, with molecular alterations in the lymphocytes that may subsequently play a role in the multi-step process of malignant lymphocyte transformation. Lymphocytes in intra-hepatic follicles in livers of patients with chronic HCV undergo an oligoclonal proliferation [41]. Circulating lymphocytes in patients with chronic HCV, but without evidence of frank lymphoma, overexpress the anti-apoptotic protein bcl-2, with a high incidence of t(14;18) translocations involving the bcl-2 gene [42]. There is also a high incidence of circulating monoclonal B cells, as evidenced by populations of lymphocytes expressing the same immunoglobulin heavy chain (IgH) rearrangements. bcl-2 and IgH rearrangements can be cleared from the blood by antiviral therapy, concurrent with suppression of the HCV, possibly eliminating the early monoclonal proliferation and preventing subsequent transformation to lymphoma [43]. Actively replicating virus has been demonstrated in HCV-associated lymphomas [44], a finding that although important does not necessarily imply a causative role of HCV.

**If HCV is lymphomagenic, how could the virus lead to malignant transformation?**

Does the presence of the virus in B lymphocytes somehow initiate cellular changes that predispose to the development of a malignant lymphoma? It is well recognized that HCV can infect B lymphocytes as discussed above. In theory, the presence of HCV proteins in infected lymphocytes could initiate growth dysregulation and predispose the lymphocyte to the development of further molecular changes, leading eventually to malignant lymphoma. No studies, however, have specifically studied the effects of the expression of HCV proteins in lymphocytes. Alternatively, does the chronic antigenic stimulation of persistent HCV infection drive lymphocyte proliferation, eventually leading to the development of a malignant lymphoma in a similar manner to that hypothesized for mucosa-associated lymphoid tissue (MALT) lymphomas and Helicobacter pylori [45]? The HCV E2 envelope protein has been identified as a potential antigen that may drive the development of lymphoma [46, 47].

Lymphoplasmacytoid lymphomas originating from the background bone marrow proliferation of EMC preferentially express certain immunoglobulin gene combinations [48], implying that this type of HCV-associated lymphoma is antigen driven. However, the majority of diffuse B-cell lymphomas associated with HCV lack any evidence of a background low-grade malignancy [24]. The method of lymphomagenesis in this and the other associated B-cell malignancies is unknown. Indeed, in these lymphomas HCV may come to be regarded as a cofactor rather than a true cause.

**Management of the lymphoma**

In areas of high background HCV prevalence, screening for HCV at diagnosis of all new B-cell malignancies is important to help direct future management, and to predict which patients may develop problems secondary to the HCV during or after treatment [49]. Patients positive for HCV antibodies should be assessed for HCV viraemia by RT–PCR, although there is no evidence linking baseline viral load and subsequent outcome of treatment. The degree of hepatitis or underlying cirrhosis should be determined, by liver biopsy, in viraemic patients with abnormal liver function tests before therapy is commenced, especially with high-dose chemotherapy.

The majority of lymphomas presenting concurrently with HCV carriage should be managed in a similar manner to their HCV-negative counterparts. For certain low-grade lymphomas there is increasing evidence that treatment of the HCV with antiviral therapy can lead to remission of the lymphoma. The underlying B-cell monoclonal proliferation associated with EMC can be cleared when the HCV is treated with interferon-α (IFN-α) [50], and there are case reports of long-lasting complete remission of frank lymphoplasmacytoid lymphoma concurrent with eradication of the virus with IFN-α [51]. Further evidence to support this approach comes from a recent case series of patients with splenic lymphoma with villous lymphocytes, with associated HCV infection and cryoglobulinaemia [52]. In this series, treatment of the HCV with IFN-α and ribavirin was followed by a complete response of the lymphoma in the majority of patients. Patients with the same lymphoma who were not infected with HCV did not respond to the IFN-α therapy. It is not clear if this approach would be applicable to other lymphomas. There are no data on the relative effectiveness of the treatment, or of the prognosis, or of other subtypes of lymphoma when associated with HCV, and they should be managed in a manner similar to their HCV-negative counterparts.

**Management of hepatitis C during treatment**

The pathogenesis of liver damage secondary to HCV is poorly understood and is a subject of substantial ongoing research. It is possible that hepatitis and liver damage is mediated in part by effects of HCV proteins, and in part by the immune response directed against the virus. The immunosuppression associated with chemotherapy upsets the balance that occurs in every chronically infected patient between viral proliferation and host immune response. During periods of lymphopenia, secondary to chemotherapy or steroids, the virus can proliferate or ‘reactivate’. After treatment is completed the immune system reconstitutes, leading to a drop in viral load, and under some circumstances this is accompanied by hepatitis. This contrasts with the hepatitis that can occur at the end of HCV antiviral therapy, which is commonly
associated with a rise in viral load. Recovery of the immune system appears to be important in the pathogenesis of liver damage secondary to chemotherapy-induced reactivation of HCV, as biochemical hepatitis usually only becomes apparent after chemotherapy is stopped. This is known as immune reconstitution hepatitis.

The risk of chemotherapy-induced proliferation of the background virus differs between HBV and HCV. Lymphoma patients undergoing immunosuppressive therapy who are hepatitis B surface-antigen positive will commonly have an immune reconstitution hepatitis. Hepatitis has been reported in 22–78% [53, 54] of cases, with a reported mortality rate of 4% [53]. Severe reactivation of HCV on the other hand is uncommon, with a severe flare of hepatitis reported in only one of 33 patients in a recent series [1]. Chemotherapy can generally be administered safely in well selected patients with background HCV infection, provided they are monitored for viral reactivation and hepatitis during therapy. Fatal fulminant hepatitis secondary to HCV has been reported on cessation of chemotherapy [2], an outcome that is unfortunately somewhat unpredictable. At the time of fulminant hepatitis the viral load is low, presumably secondary to the immune response. The HCV viral load at the time of reconstitution hepatitis is therefore an unreliable test to help differentiate potential causes of the hepatitis.

Bone marrow transplantation in patients with chronic HCV is associated with a higher incidence of veno-occlusive disease, especially in cirrhotic patients [55]. Following transplantation, patients with HCV subsequently have a high long-term risk of developing cirrhosis [56]. No studies have examined whether suppression of the HCV before chemotherapy or bone marrow transplantation improves outcome. It is possible that patients at high risk of viral proliferation and immune reconstitution hepatitis may benefit from suppression of the virus with IFN-α and ribavirin, although this would be at the expense of exacerbated immunosuppression.

**Conclusion**

Despite controversy in the literature, epidemiological evidence strongly suggests a link between chronic infection with hepatitis C and B-cell NHL in high prevalence areas. The absolute risk of developing lymphoma when infected with hepatitis C appears to be low, and hepatitis C only contributes significantly to the incidence of lymphoma in countries with a high prevalence of the virus in the population. Increasing molecular evidence of the pathogenesis of hepatitis C-associated lymphoma supports the epidemiological evidence. Viral reactivation with chemotherapy and immune reconstitution hepatitis can complicate treatment of these lymphomas. In high prevalence areas, screening for the virus should be considered at diagnosis. There is increasing evidence that treatment of the underlying HCV infection can lead to regression of some low-grade lymphomas.

**References**


