

# REVIEWS IN BASIC AND CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

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## Extrahepatic Morbidity and Mortality of Chronic Hepatitis C



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Chronic hepatitis C virus (HCV) infection is associated with several extrahepatic manifestations. Patients with HCV may develop mixed cryoglobulinemia and its sequelae, ranging from cutaneous and visceral vasculitis to glomerulonephritis and B-cell non-Hodgkin lymphoma. HCV-infected patients have increased rates of insulin resistance, diabetes, and atherosclerosis, which may lead to increased cardiovascular morbidity and mortality. Neurological manifestations of HCV infection include fatigue and cognitive impairment. The mechanisms causing the extrahepatic effects of HCV infection are likely multifactorial and may include endocrine effects, HCV replication in extrahepatic cells, or a heightened immune reaction with systemic effects. Successful eradication of HCV with interferon alfa and ribavirin was shown to improve some of these extrahepatic effects; sustained virological response is associated with resolution of complications of cryoglobulinemia, reduced levels of insulin resistance, reduced incidence of diabetes and stroke, and improved fatigue and cognitive functioning. The availability of new interferon-free, well-tolerated anti-HCV treatment regimens is broadening the spectrum of patients available for therapy, including those in whom interferon was contraindicated, and will likely result in greater improvements in the extrahepatic manifestations of HCV. If these regimens are shown to confer significant benefit in the metabolic, cardiovascular, or neuropsychiatric conditions associated with HCV infection, extrahepatic manifestations of HCV may become a major indication for treatment even in the absence of liver disease.

**Keywords:** Cryoglobulins; Insulin Resistance; Cardiovascular Risk; Fatigue; Health-Related Quality of Life.

Treating patients who are chronically infected with hepatitis C virus (HCV) to eradicate the infection and achieve sustained virological response (SVR; undetectable HCV RNA 12 or 24 weeks after completion of therapy) decreases the risk of cirrhosis, liver failure, and hepatocellular carcinoma (HCC).<sup>1–3</sup> In addition to liver-related sequelae, chronic HCV infection is associated with changes in organ systems outside the liver, including metabolic, cardiovascular,

and neurological systems, and with autoimmune and immune-mediated conditions such as mixed cryoglobulinemia (MC), thyroid disease, and glomerulonephritis.<sup>4–7</sup> A large, prospective cohort study found that patients with chronic HCV infection, defined as having detectable HCV RNA in serum, have an elevated risk of death from both hepatic and nonhepatic diseases, including cardiovascular and renal diseases, compared with uninfected patients and those with antibodies to HCV (anti-HCV) but no detectable HCV RNA in serum.<sup>8</sup> These and other findings raise the question of whether successful treatment of chronic HCV infection may also improve the associated extrahepatic effects and reduce nonhepatic morbidity and mortality. One multicenter international study has already shown that achieving SVR reduces not only liver-related but also all-cause and non-liver-related mortality.<sup>9</sup>

The mechanisms causing the extrahepatic effects of HCV are incompletely understood. HCV drives clonal expansion of B cells<sup>10,11</sup> to generate immunoglobulin (Ig) M rheumatoid factor in susceptible people that results in immune complex deposition in small vessels and vasculitis, although susceptibility factors are unknown. The mechanisms of other manifestations are multifactorial, including a direct interaction between viral proteins and intracellular signaling pathways, viral replication in extrahepatic cells, or a heightened immune reaction with systemic effects. Immune activation may lead to a chronic inflammatory state that can affect a number of systems, as has been observed in human immunodeficiency virus (HIV) infection.<sup>12</sup> Like HIV, HCV infection is associated with decreased quality of life<sup>13</sup>; the most important driving factors are fatigue,

**Abbreviations used in this paper:** anti-HCV, antibodies to hepatitis C virus; CI, confidence interval; CNS, central nervous system; DAA, direct-acting antiviral; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HOMA-IR, homeostasis model for assessment of insulin resistance; HR, hazard ratio; HRQOL, health-related quality of life; Ig, immunoglobulin; MC, mixed cryoglobulinemia; NHL, non-Hodgkin lymphoma; NS3, nonstructural 3; OR, odds ratio; PCT, porphyria cutanea tarda; SVR, sustained virological response.

Most current article

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0016-5085/\$36.00

<http://dx.doi.org/10.1053/j.gastro.2015.08.035>

depression, and cognitive impairment.<sup>14</sup> There is evidence that treatment to eradicate HCV infection may improve some extrahepatic manifestations of HCV independently of the severity of the underlying liver disease. The evidence is strongest for MC, which often resolves entirely with viral clearance.<sup>15–17</sup>

In the era of interferon-based treatment, extrahepatic manifestations of HCV were frequently regarded as contraindications to treatment because treatment could exacerbate the manifestations, or because ongoing treatment of coexisting extrahepatic syndromes could result in untoward drug-drug interactions or additional toxicities. Patients with a history of autoimmune disease or psychological instability, for example, are often ineligible for interferon-containing regimens.<sup>18,19</sup> Recent advances in anti-HCV therapy have led to well-tolerated, interferon-free regimens, such that more patients may be treated, leading to the potential for improvements in extrahepatic manifestations on a larger scale. Quality of life previously decreased during antiviral therapy, but interferon-free therapies may improve quality of life while patients are on treatment<sup>20,21</sup> and allow treatment where previously contraindicated.<sup>22</sup> This review will consider the impact of chronic HCV infection on sites outside the liver, focusing on immunologic, metabolic, cardiovascular, and neurological manifestations.

## Metabolic Manifestations of HCV Infection

### *Diabetes Mellitus and Insulin Resistance*

Several studies have shown that patients with chronic HCV infection have an increased risk of diabetes mellitus compared with uninfected people (Table 1).<sup>5,6,23</sup> White et al showed that HCV infection is associated with an increased risk of diabetes in comparison to both uninfected and hepatitis B virus (HBV)-infected controls, suggesting that HCV plays a specific role in conferring the increased risk of diabetes.<sup>24</sup> The elevated risk is likely due to an association between HCV and insulin resistance. Recent data suggest that HCV-induced liver inflammation may significantly increase this risk,<sup>25,26</sup> and the observation that increased levels of liver enzymes, rather than HCV infection, is the true risk factor for development of diabetes in the HCV-infected US population<sup>27</sup> should be interpreted in view of these findings.

HCV-infected patients have significantly higher levels of insulin resistance (as measured by the homeostasis model for assessment of insulin resistance [HOMA-IR]) than uninfected controls or HBV-infected patients matched for body mass index, waist circumference, age, and sex (Table 1).<sup>28,29</sup> However, the evidence in favor of a viral dose effect is weak; although patients with a higher viral load tend to have higher levels of insulin resistance,<sup>29–31</sup> the correlation between HOMA-IR score and HCV RNA level is on average very weak or absent.<sup>32,33</sup> Similarly, there is no consistently reported genotype specificity associated with HOMA-IR scores.<sup>34–37</sup>

The most compelling evidence that HCV causes insulin resistance is the observation that curing HCV with antiviral therapy results in reduced levels of insulin

resistance, whereas levels remain unchanged in virological nonresponders.<sup>38</sup> A phase 1 study of an interferon-free short course of danoprevir, an inhibitor of the HCV nonstructural 3 (NS3) serine protease, showed a close correlation between decline in viral load and reduction of HOMA-IR scores.<sup>39</sup> This suggests that treatment with HCV protease inhibitors or other anti-HCV direct-acting antivirals (DAAs) may restore insulin sensitivity in patients with chronic HCV infection.

### *Mechanisms of HCV-Induced Insulin Resistance*

HCV may directly interfere with the insulin signaling pathway. This is suggested by the finding that nonobese, nondiabetic, HCV-infected patients have hepatic insulin resistance, as determined by the hyperinsulinemic-euglycemic clamp technique. Two different studies showed that endogenous glucose production in such patients was incompletely suppressed by low-dose insulin.<sup>34,40</sup> In one study, the hepatic insulin resistance index increased by a factor of 3 compared with healthy controls.<sup>34</sup> When liver samples from HCV-infected patients and uninfected controls were challenged with insulin *ex vivo*, the insulin-induced activation of the protein kinase B/Akt (PKB/Akt), the key kinase responsible for most metabolic effects of insulin, was blunted in HCV-infected cells compared with controls.<sup>41</sup> According to experimental models, the HCV core protein seems sufficient to induce insulin resistance via several postreceptorial mechanisms.<sup>42</sup>

In addition to hepatic insulin resistance, however, peripheral insulin resistance is elevated in HCV infection and appears to be the most important component of HCV-associated whole body insulin resistance.<sup>34,40</sup> An increased peripheral insulin resistance was reported independently by the 2 previously cited groups that used a hyperinsulinemic-euglycemic clamp in nonobese, normoglycemic, HCV-infected patients.<sup>34,40</sup> Using high concentrations of insulin, glucose uptake and oxidative consumption were impaired, implying a deficient glucose transport and disposal, accounted for by striated muscle. Interestingly, this viral-associated insulin resistance does not appear to involve increased free fatty acid efflux from adipose tissue, which remains normally sensitive to insulin.<sup>34,40</sup> Thus, glucose uptake is clearly impaired in patients with HCV infection.

Finally, HCV-induced liver inflammation<sup>25,26</sup> may increase the risk of developing insulin resistance via the release of proinflammatory cytokines, such as tumor necrosis factor  $\alpha$  and interleukin-6, which may in turn interfere with the insulin signaling transduction pathway in hepatocytes.<sup>43</sup>

In summary, HCV causes hepatic and extrahepatic insulin resistance. Although hepatic impairment of the effects of insulin may be mediated by direct interactions in infected hepatocytes, increased peripheral insulin resistance may be caused by endocrine effects of soluble mediators secreted by infected hepatocytes. These soluble mediators may also increase hepatic insulin resistance via paracrine mechanisms. They may exert their peripheral effects by reducing glucose uptake and oxidative consumption by extrahepatic tissues, specifically muscle and, probably to a lesser extent, adipose tissue.<sup>34,40</sup> The factors involved in the paracrine

**Table 1.** Metabolic Effects of HCV Infection

Potential effect	Studies and main findings	Reference
Diabetes mellitus	Mehta et al, 2000: Based on NHANES data collected between 1988 and 1994, among patients 40 years of age and older, HCV infection was associated with diabetes (OR, 3.77; 95% CI, 1.80–7.87)	5
	Wang et al, 2007: Compared with uninfected people, HCV-infected patients had a higher cumulative incidence of diabetes (HR, 1.7; 95% CI, 1.3–2.1) in a community-based longitudinal study	6
	Mehta et al, 2003: Among patients at high risk for diabetes, HCV infection increased the risk of diabetes more than 11-fold during 9 years of follow-up (HR, 11.58; 95% CI, 1.39–96.6)	23
	Younossi et al, 2013: Based on NHANES data collected between 1999 and 2010, chronic HCV infection was independently associated with diabetes (OR, 2.31; 95% CI, 1.18–4.54), insulin resistance (OR, 2.06; 95% CI, 1.19–3.57), and hypertension (OR, 2.06; 95% CI, 1.30–3.24)	28
	White et al, 2008: HCV-infected patients had a significantly higher risk of diabetes compared with uninfected controls and compared with HBV-infected controls in a meta-analysis	24
Insulin resistance	Younossi et al, 2013: Based on NHANES data collected between 1999 and 2010, chronic HCV was independently associated with diabetes (OR, 2.31; 95% CI, 1.18–4.54), insulin resistance (OR, 2.06; 95% CI, 1.19–3.57), and hypertension (OR, 2.06; 95% CI, 1.30–3.24)	28
	Moucari et al, 2008: Insulin resistance (HOMA-IR) was present in 35% of HCV-infected vs 5% of HBV-infected patients and was associated with HCV genotypes 1 and 4, high viral load, and liver fibrosis	29
	Vanni et al, 2009: Patients with chronic HCV infection and no features of metabolic syndrome (n = 14) showed increased peripheral and hepatic insulin resistance compared with healthy controls (n = 7); hepatic insulin resistance index was increased 3-fold in HCV-infected patients compared with controls	34
	Milner et al, 2010: Insulin resistance was significantly increased in nonobese, HCV-infected male patients compared with healthy controls; insulin resistance was principally peripheral rather than hepatic, most likely in muscle	40
	Muzzi et al, 2005: HOMA-IR score was associated with fibrosis in HCV-infected patients	36
	Lecube et al, 2006: In a case-control study, HOMA-IR score was significantly higher in HCV-infected patients than in controls with chronic hepatitis other than HCV	156

NHANES, National Health and Nutrition Examination Survey.

and endocrine propagation of insulin resistance are currently unknown. In addition to tumor necrosis factor  $\alpha$ , other candidate cytokines include interleukin-8,<sup>44,45</sup> chemokine (C-C) motif ligand 2 (CCL2),<sup>45</sup> interleukin-18,<sup>34</sup> chemerin,<sup>46</sup> and visfatin.<sup>47</sup>

### Insulin Resistance and Outcomes

HCV-associated insulin resistance is correlated with poor outcomes, including accelerated progression of hepatic fibrosis, reduced SVR rates, and the development of HCC and type 2 diabetes mellitus and its cardiovascular sequelae.<sup>48–51</sup> There is no clear evidence that insulin resistance promotes HCV replication; treatment of chronic HCV with insulin sensitizers such as pioglitazone has been shown to reduce insulin resistance but not to reduce viremia.<sup>52</sup> However, among patients with chronic HCV infection who have minimal or no fibrosis (F0–F1), the HOMA-IR score was independently associated with the progression of fibrosis.<sup>48</sup> Higher HOMA-IR scores have also been shown to be associated with lower SVR rates in patients treated with interferon, independently of HCV genotype.<sup>49,50,53–55</sup> Finally, a large retrospective study showed that among HCV-infected patients, the presence of type 2 diabetes mellitus increases the incidence of HCC nearly 2-fold compared with nondiabetic patients.<sup>56</sup> Controlling glycemia seems to make a difference; there was a higher incidence of HCC in patients with hemoglobin A<sub>1c</sub>  $\geq 7\%$  than among those with hemoglobin A<sub>1c</sub>  $< 7\%$ .

In contrast to its effect on outcomes with interferon-based treatment, insulin resistance appears to have no effect on outcomes after treatment with DAAs. A study of danoprevir monotherapy showed that the rate of HCV RNA decline is not associated with baseline HOMA-IR scores,<sup>39</sup> and 2 studies using telaprevir-based regimens showed that HOMA-IR scores fail to predict virologic end points, including SVR.<sup>57,58</sup> However, telaprevir-based regimens still contain peginterferon and ribavirin. The availability of DAAs may enable the successful treatment of more HCV-infected patients, because even those previously classified as difficult to treat due to baseline insulin resistance may have improved outcomes with new therapies that do not include interferon.

## Cardiovascular Manifestations of HCV Infection

### HCV as a Cardiovascular Risk Factor

Despite the association of HCV with insulin resistance, type 2 diabetes mellitus, and hepatic steatosis, it is still unclear whether HCV is an independent risk factor for cardiovascular disease.<sup>59</sup> HCV-infected patients have significantly lower levels of total cholesterol, low-density lipoprotein, and triglycerides and higher levels of high-density lipoprotein than uninfected people,<sup>60,61</sup> thus showing what has been called a cardioprotective lipid

profile. Nevertheless, data from several studies show an association between HCV infection and atherosclerotic changes. A case-control study showed that the prevalence of HCV positivity is significantly higher among patients with angiographically documented coronary artery disease (>50% stenosis) than among controls (patients hospitalized for other cardiac abnormalities) and that the prevalence of HCV increases with the number of arteries affected.<sup>62</sup> On multivariate analysis, HCV seropositivity was identified as an independent predictor of coronary artery disease, with an odds ratio (OR) of 4.2 (95% confidence interval [CI], 1.4–13.0). Another study showed that HCV infection is an independent predictor of the severity of coronary atherosclerosis, with an OR of 2.0 (95% CI, 1.6–2.6).<sup>63</sup> Studies of changes in the carotid arteries have yielded similar results, showing an association of HCV infection with early, asymptomatic carotid atherosclerosis, as indicated by carotid intima-media thickness and the presence of plaques.<sup>64,65</sup> The HCV viral load is independently associated with carotid atherosclerosis, suggesting a causal link between the level of HCV infection and atherosclerotic changes.<sup>32</sup> Accordingly, a study reported that the risk of peripheral artery disease in patients with HCV infection is higher than in uninfected patients, especially in the presence of comorbidities.<sup>66</sup>

Consistent with the association of HCV with atherosclerosis, rates of cardiovascular events and mortality may be elevated among HCV-infected patients. A retrospective study of first-time blood donors showed increased rates of overall and cardiovascular mortality among anti-HCV-positive compared with anti-HCV-negative individuals, with a hazard ratio (HR) of 2.21 (95% CI, 1.41–3.46).<sup>67</sup> A recent prospective study confirmed these findings, showing that HCV-infected patients have increased hepatic and extrahepatic mortality, including increased mortality from circulatory diseases (HR, 1.50; 95% CI, 1.10–2.03).<sup>8</sup> Further, among anti-HCV-positive patients, the increased mortality from circulatory diseases held for patients with detectable HCV RNA but not for those with undetectable HCV RNA, suggesting a causal connection between the virus and circulatory mortality. A recent cohort study in Taiwan found that chronic HCV infection is an independent predictor of stroke, with an adjusted HR of 1.27 (95% CI, 1.14–1.41), and a community-based prospective study found that chronic HCV infection is an independent predictor of cerebrovascular death, with a significant association between cerebrovascular mortality and increasing serum HCV RNA levels.<sup>68,69</sup>

However, some studies have found no association between HCV infection and cardiovascular disease. A large retrospective study in the United Kingdom showed no difference in the incidence of acute myocardial infarction between HCV-infected and -uninfected patients,<sup>70</sup> and a case-control study of active-duty US military personnel similarly found no association between HCV and myocardial infarction.<sup>71</sup> Several cross-sectional and longitudinal studies have shown the lack of an independent association of HCV with the incidence or severity of atherosclerosis.<sup>72,73</sup> The contradictory findings regarding HCV infection and cardiovascular disease may be due to differences in the characteristics of

populations studied or in the assessment of end points or adjustments for confounding factors. In addition, stratification for the prevalence of well-known cardiovascular risk factors such as smoking, diabetes, and hypertension could help to better understand the reported conflicting results and to identify groups of patients in which the effect of HCV on cardiovascular risk is further pronounced.

### *Potential Mechanisms of Cardiovascular Effects*

The potential association between HCV infection and cardiovascular risk raises the question of the mechanism underlying this association. Metabolic factors may play a role; the insulin resistance associated with HCV leads to hyperglycemia, endothelial dysfunction, and inflammation, all of which produce vessel damage and unstable plaques. Perticone et al recently showed a significant correlation between insulin resistance and left ventricular mass among normotensive patients with HCV infection, and a strong relationship between HCV viral load and both of these parameters.<sup>74</sup> The presence of HCV may also induce a chronic inflammatory state with systemic effects. In support of this, in a myocardial scintigraphy study of HCV-infected patients, Maruyama et al found that 87% had myocardial perfusion defects and that the severity of the defects was associated with the degree of liver necroinflammatory activity.<sup>75</sup> These findings suggest that the proinflammatory environment leading to necrosis and consequently fibrosis in the liver also has systemic effects, leading to atherosclerosis in the vessels. Consistent with this suggestion, Petta et al found that severe hepatic fibrosis (F3/F4 vs F1/F2) was independently associated with the development of carotid plaque in HCV-infected patients.<sup>65</sup>

### *HCV and Cardiovascular Outcomes*

If active HCV infection is associated with cardiovascular risk, then eradication of HCV might reduce that risk and reduce the incidence of cardiovascular events. Some studies have shown such a connection. In the previously mentioned myocardial scintigraphy study, successful suppression of HCV RNA during treatment and eradication after treatment with interferon-based therapy was associated with improvements in the baseline myocardial perfusion defects.<sup>75</sup> Moreover, among patients who experienced a relapse, there was initial improvement during suppression of HCV RNA and then worsening of the perfusion defects at the time of reappearance of the virus; among nonresponders, no change in perfusion defects was observed. Regarding cardiovascular events, a large, retrospective cohort study found that interferon-based therapy significantly reduced the incidence of stroke compared with no treatment (adjusted HR, 0.39; 95% CI, 0.16–0.95),<sup>76</sup> suggesting the potential long-term extrahepatic benefits of successfully treating HCV infection. Consistent with these results, a recent study of Taiwanese patients with HCV infection showed that interferon-based treatment significantly reduced the incidence of end-stage renal disease, acute coronary syndrome, and ischemic stroke.<sup>77</sup>

## Neurological Manifestations of HCV Infection

### Neuropsychiatric Symptoms Associated With HCV

Chronic HCV infection is associated with psychiatric comorbidities. Fatigue, depression, anxiety, bipolar disorder, and schizophrenia are all more prevalent among HCV-infected patients than the general population.<sup>78</sup> This is partly related to the higher incidence of risk behaviors among people with psychiatric disorders, which can result in HCV exposure and increased alcohol use.<sup>79</sup> However, emerging literature shows that HCV is also associated with an increased prevalence of neuropsychiatric symptoms, independent of preexisting mental disorders or high-risk behaviors (Table 2). HCV-infected patients have a significantly reduced quality of life, as manifested by physical symptoms including fatigue, energy level, and physical functioning, compared with both uninfected and HBV-infected controls.<sup>80</sup> Moreover, this reduced quality of life could not be attributed to cirrhosis because patients with cirrhosis were excluded from the study, and this was found to hold true for patients with or without a history of substance abuse and with either mild or severe liver necroinflammation. Thus, the symptoms causing reduced quality of life appeared to be due to the presence of HCV, regardless of the mode of acquisition of HCV or the severity of liver disease. In subsequent larger studies, the mental aspects of health-related quality of life (HRQOL) appeared to be specifically impaired in HCV infection compared with primary biliary cirrhosis, in which physical well-being was more impaired.<sup>81</sup>

Fatigue and cognitive impairment have both been associated with HCV infection and are in part responsible for reduced quality of life. Fatigue is the most common symptom, reported by more than 50% of HCV-infected patients.<sup>82–84</sup> Fatigue does not appear to be associated with HCV RNA level, HCV genotype, or liver histology. In one study, HCV-associated fatigue was found to be associated with female sex and age older than 50 years.<sup>82</sup> In addition to fatigue, impaired cognition is also reported, often referred to by HCV-infected patients as a feeling of “brain fog.” Indeed, studies have shown mild but significant neurocognitive impairment in a proportion of HCV-infected patients with minimal or absent liver disease.<sup>85,86</sup> In one study, in an attempt to control for factors related to modes of HCV acquisition, Forton et al compared HCV-infected viremic patients who had histologically mild disease with patients who had prior HCV infection and had cleared the virus.<sup>85</sup> HCV-infected viremic patients showed greater cognitive impairment on formal testing than those with resolved infection, and the deficits were shown specifically in concentration and speed of working memory. Because patients with advanced fibrosis or cirrhosis were excluded from the study, the impairments could not be accounted for by mild hepatic encephalopathy. Moreover, the cognitive impairment was found to be independent of a history of substance abuse, depression, fatigue, or symptom severity. Thus, cognitive impairment appeared to be associated with the presence of HCV, independent of how the infection was acquired or the presence of other neuropsychiatric symptoms.

Other studies have also shown HCV-associated cognitive impairment, reporting deficits in measures of

**Table 2.** Neurological Effects of HCV Infection

Potential effect	Studies and main findings	Reference
Fatigue	Foster et al, 1998: HCV-infected patients had significantly reduced quality of life compared with uninfected and HBV-infected controls, as measured by physical functions (fatigue, energy, body pain) assessed using the Short Form 36 symptomatology questionnaire	80
	Poynard et al, 2002: Fatigue was present in 53% of HCV-infected patients and was associated with female sex, age older than 50 years, cirrhosis, depression, and purpura	82
	Cacoub et al, 2002: Fatigue was present in 59% of patients with chronic hepatitis C	83
	Stefanova-Petrova et al, 2007: Fatigue was present in 60% of HCV-infected patients	84
	Tillmann et al, 2011: Two independent prospective cross-sectional studies of 511 and 284 patients with different forms of liver disease showed reduced mental quality of life in HCV-infected patients	81
	Forton et al, 2002: Patients with chronic hepatitis C who have detectable HCV RNA and histologically mild disease were cognitively impaired compared with previously infected patients who had cleared the virus and compared with healthy controls; HCV-infected patients were significantly impaired on tests of concentration and speed of memory processes	85
Cognitive impairment	Weissenborn et al, 2004: HCV-infected patients with mild liver disease showed impairment in attention and higher executive function compared with healthy controls	86
	Hilsabeck et al, 2002 and 2003: Cognitive impairment in patients with HCV was related to severity of liver disease but was also evident in patients without cirrhosis	7, 88
	Letendre et al, 2005: HIV, HCV, and methamphetamine use were independently associated with cognitive impairment in HCV/HIV-coinfected patients	89
	Weissenborn et al, 2006: Decreased serotonin and dopamine transporter binding, measured by single-photon emission computerized tomography, was associated with impaired performance on psychometric testing	96
	Forton et al, 2008: Impairments in working memory correlated with white matter myoinositol/creatine ratios, measured by cerebral magnetic resonance spectroscopy	93

immediate and sustained attention, higher executive function, verbal learning ability, recall, and working memory.<sup>87</sup> HCV-infected patients with mild liver disease showed deficits in attention and higher executive function compared with healthy controls, and the deficits were associated with severity of fatigue.<sup>86</sup> Although the HCV-infected patients in that study were also more depressed and anxious than the healthy controls, the selective nature of the cognitive deficits made it unlikely that the depression caused the cognitive impairment. Hilsabeck et al found a significant relationship between cognitive test performance and fibrosis stage on liver biopsy in HCV-infected patients; however, patients with minor hepatic injury also showed cognitive dysfunction in the attention and concentration domains, with impairment found in up to 50% of noncirrhotic, HCV-infected patients.<sup>7,88</sup> The pattern of impairment was similar to that found in other studies and was believed to be consistent with frontal-subcortical dysfunction, which parallels findings in HIV infection. Indeed, HCV infection appears to be an important independent factor for cognitive impairment in HCV/HIV-coinfected patients.<sup>87</sup> For example, in a large prospective cohort of 526 patients, HIV, HCV, and methamphetamine use were independently associated with worse cognitive impairment, and higher HCV viral loads were positively correlated with impaired memory.<sup>89</sup>

In summary, a number of studies show that patients with histologically mild hepatitis C have evidence of cognitive impairment and exhibit symptoms of fatigue, and these neuropsychiatric manifestations appear to be independent of a history of substance abuse or the presence of mood disorders. Although HCV infection is often accompanied by advanced liver disease, illicit drug use, and other factors that may have additional effects on cognitive function, the reported findings suggest that HCV infection itself may have a direct biological effect on the central nervous system (CNS).

### *Evidence for a Biological Effect on the CNS*

To determine whether a biological process underlies the neuropsychiatric symptoms and deficits associated with HCV, brain imaging has been used. Using proton magnetic resonance spectroscopy, several groups have shown that HCV-infected patients with mild or absent liver disease and cognitive impairment have altered cerebral metabolism.<sup>85,86,90</sup> Cerebral proton magnetic resonance spectroscopy has shown that HCV-infected patients have elevated levels of choline in certain brain regions (basal ganglia, white matter, occipital grey matter) and reduced levels of *N*-acetylaspartate compared with uninfected people.<sup>86,90–92</sup> These observed changes were not associated with the severity of liver disease and could not be attributed to hepatic encephalopathy. More recently, in separate studies by Bokemeyer et al and Forton et al, HCV-infected patients were shown to have elevated myoinositol/creatine ratios in the white matter that, in one study, were statistically correlated with impairments in working memory.<sup>92,93</sup> These findings strongly suggest that HCV infection causes brain dysfunction.

One possible mechanism by which HCV may result in brain dysfunction is by inducing neuroinflammation. Elevated choline and myoinositol levels, shown in the studies described in the preceding text, are also observed in neuroinflammatory conditions such as multiple sclerosis or HIV infection of the brain and are consistent with CNS glial cell proliferation and cell membrane injury, respectively.<sup>94</sup> The altered cerebral metabolism observed in patients with chronic hepatitis C suggests that active HCV infection might result in cerebral immune activation. Further evidence for this hypothesis comes from cerebral positron emission tomography imaging using PK11195, a ligand to the peripheral benzodiazepine receptor or translocator protein, which is expressed on activated microglia. In a study of patients with histologically mild HCV infection, PK11195 binding potential was significantly increased in the caudate nucleus of HCV-infected patients compared with healthy controls, and this was positively correlated with viral load.<sup>95</sup> The HCV-infected patients in this study also showed elevated myoinositol/creatine and choline/creatine ratios compared with healthy controls. Thus, both altered cerebral metabolism and increased microglial activation were observed in patients with mild hepatitis C, and the microglial activation was associated with HCV viremia. These results may indicate that HCV in the CNS induces neuroinflammation. Abnormalities in cerebral glucose metabolism and neurotransmission have also been reported in patients with noncirrhotic HCV infection, suggesting that the neuroinflammatory process leads to functional deficits.<sup>96,97</sup>

HCV may cause neuroinflammation by penetrating the CNS and replicating in brain tissue. Evidence for this hypothesis comes from studies using molecular virology and laser capture microdissection techniques in autopsy samples.<sup>98,99</sup> In one study, HCV NS3 protein was found in brain microglia and, less often, in astrocytes.<sup>98</sup> Viral sequences isolated from the CNS are distinct from those in serum and liver and share similarities from sequences associated with or isolated from peripheral blood mononuclear cells. Another study compared autopsy brain tissue from 7 HCV-positive and 8 HCV-negative patients and found that microglia of HCV-positive patients expressed higher levels of proinflammatory cytokines than HCV-negative controls; similarly, when microglia that costained for NS3 were compared with HCV-negative cells in each of the 7 HCV-positive patients, the NS3-positive cells expressed higher levels of proinflammatory cytokines.<sup>100</sup> These data suggest that viral penetration into the CNS may directly result in microglial activation that in turn may trigger pathways that ultimately result in disturbances in neurotransmission.

An alternative mechanism for the neuropsychiatric manifestations of HCV infection might be the effect of peripheral inflammation across the blood-brain barrier. Tryptophan, a serotonin precursor, is metabolized by the enzyme indoleamine 2,3-dioxygenase, producing kynurenine. Indoleamine 2,3-dioxygenase is activated by proinflammatory cytokines, including the interferons, and its activity can be estimated by measuring the ratio of blood concentrations of kynurenine and tryptophan. Wichers et al showed that in HCV-infected patients treated with interferon, the

development of depressive symptoms is associated with elevated kynurenine/tryptophan ratios and the production of neurotoxic metabolites.<sup>101</sup> Whether endogenous cytokines might have the same effect is not known, but in a pilot study of untreated HCV-infected patients, the kynurenine/tryptophan ratio was significantly elevated in fatigued patients compared with both HCV-infected, nonfatigued patients and uninfected controls.<sup>102</sup>

The issue of extrahepatic replication of HCV remains controversial, but recent work has shown that brain microvascular endothelial cells express all the receptors necessary for HCV infection and also permit HCV replication; the endothelial cells were shown to release infectious virus and to undergo conformational changes, which might allow viral passage across the blood-brain barrier.<sup>103</sup> One hypothesis that may explain the findings to date is that HCV may infect the brain endothelium, resulting in apoptosis and a leaky blood-brain barrier, which in turn would allow peripheral cytokine and perhaps viral entry into the CNS (Figure 1A).<sup>104</sup> Thus, the hypothesis is that HCV enters the brain and causes neuroinflammation, leading to HCV-associated neuropsychiatric symptoms.

Consistent with the suggestion that there is a biological etiology for HCV-associated cognitive dysfunction, Kraus et al showed that successful HCV eradication with peginterferon and ribavirin was associated with improved attention, vigilance, and working memory, while virological nonresponders showed no such improvements.<sup>105</sup> These improvements in cognitive function were shown 1 year after the end of treatment to control for the known effect of interferon-based treatment on brain function during the treatment period.<sup>106</sup> Most recently, a pilot study in a small group of patients, using magnetic resonance spectroscopy, showed normalization of cerebral *N*-acetylaspartate levels, interpreted as recovery of neuronal dysfunction after successful antiviral treatment with interferon-free therapy.<sup>107</sup>

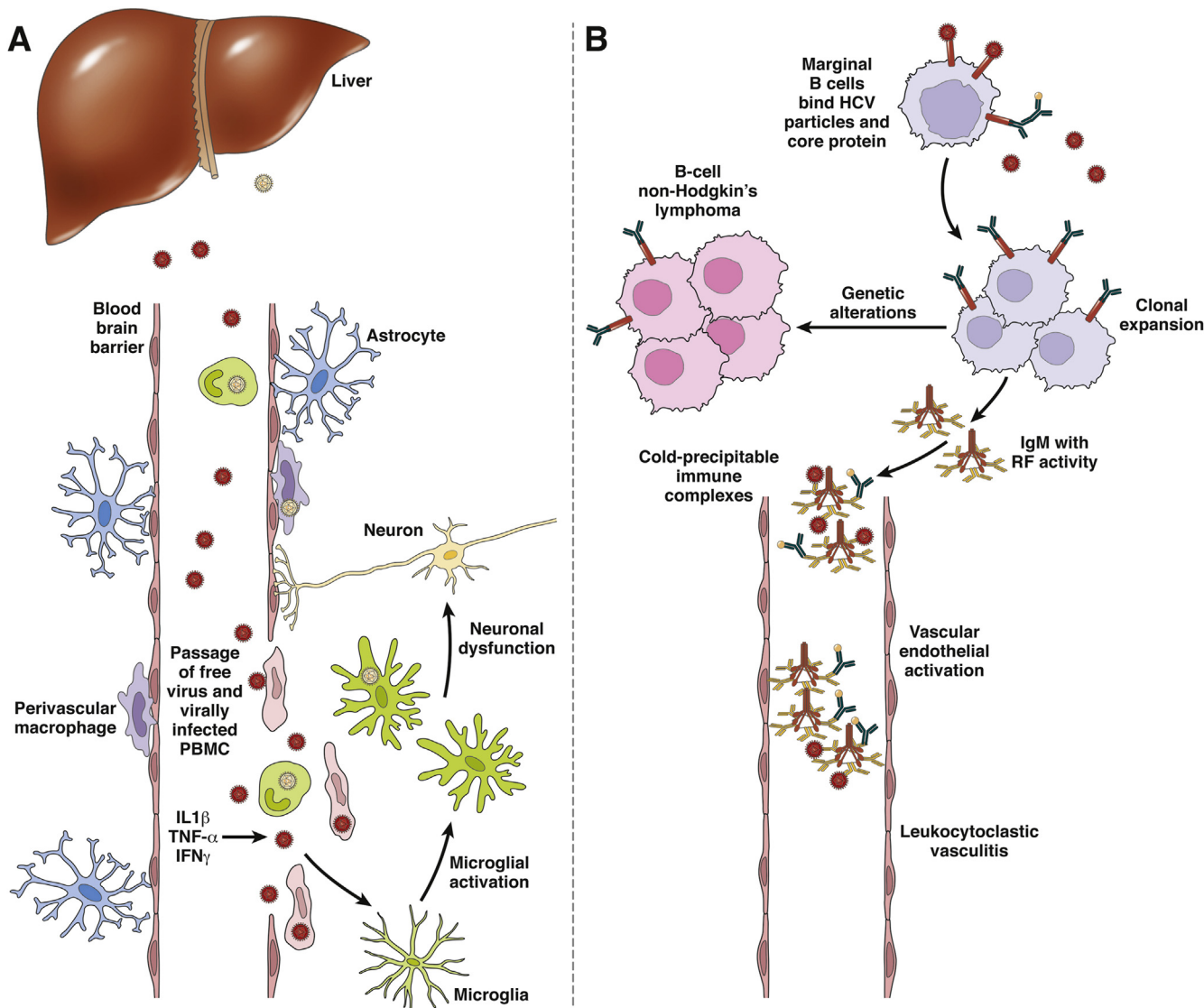
## HCV, MC, and Non-Hodgkin Lymphoma

Shortly after the discovery of HCV, it was recognized that a high proportion of patients with MC were infected with the newly identified virus.<sup>108</sup> Subsequent studies confirmed that up to 91% of patients with MC have active HCV infection.<sup>109,110</sup> Circulating cryoglobulins are found in 40% to 60% of HCV-infected patients; however, only 5% to 10% of these patients develop clinical consequences.<sup>111</sup> Clinical manifestations vary widely in prevalence and severity, with many patients having no symptoms and others presenting with life-threatening systemic vasculitis. Cutaneous vasculitis with palpable purpura, often on the anterior aspect of the lower extremities, occurs in 18% to 33% of patients and ranges from asymptomatic pigmentation from hemosiderosis related to past active small-vessel vasculitis to aggressive cutaneous ulceration.<sup>17</sup> Renal involvement with membranoproliferative glomerulonephritis occurs in approximately 27% of patients, ranging from mild proteinuria to progressive renal impairment. Other symptoms include neuropathy (11%–30%), sicca syndrome (10%–25%), and

arthralgias (35%–54%) as well as nonspecific features such as fatigue (50%).<sup>112</sup>

Although there is accumulating evidence that HCV is able to infect and replicate in B cells, it is not clear that lymphocyte infection is required for MC to develop.<sup>113</sup> Clonal expansion of B cells in response to viral antigens leads to production of rheumatoid factor-containing immune complexes, which cause symptomatic disease due to a complement C1q-mediated vasculitis on deposition in small vessels of different organs (Figure 1B).<sup>17</sup> Demonstration that the cryoprecipitate contains viral antigens, particularly the core protein, along with the expected monoclonal IgM, polyclonal IgG, and complement proteins, furthered the evidence supporting a direct link between HCV and MC.<sup>17</sup> HCV may stimulate B-cell proliferation through direct interaction of the HCV E2 glycoprotein with CD81 on the surface of B cells or may directly bind to and activate HCV-specific B-cell receptors.<sup>114</sup> B cells in patients with MC show a restricted Ig heavy chain use, with *V<sub>H</sub>1-69* and *V<sub>K</sub>3-20* highly over-represented.<sup>10</sup> Notably, these same clonal populations are found in patients with HCV-associated non-Hodgkin lymphoma (NHL), suggesting a strong link between these 2 lymphoproliferative conditions.<sup>11</sup> However, even among patients with MC, NHL is rare, occurring at a rate of 6.6 per 1000 person-years or less; this suggests that NHL requires a second event beyond clonal B-cell expansion.<sup>115</sup> This is supported by careful evaluation of the B-cell populations. Patients with MC show expansion of peripheral IgM<sup>+</sup>κ<sup>+</sup>CD27<sup>+</sup> B cells, characteristic of memory B cells.<sup>10</sup> Phylogenetic analysis suggests antigen-driven affinity maturation, supporting the concept that these cells are responding to viral antigens.<sup>17</sup> However, transcriptional analysis has shown that many of the B cells in patients with MC display an anergic and proapoptotic phenotype, suggesting a loss of antigen-driven proliferation, possibly as a feedback mechanism to prevent autoreactive B-cell responses and explaining the relatively low frequency of clinical manifestations in patients.<sup>116</sup> Loss of the proapoptotic phenotype through specific gene translocations, stimulation by B-cell activating factor, and other mechanisms may lead MC to give rise to low-grade NHL.<sup>112</sup> HCV is also associated with aggressive diffuse large B-cell NHL; however, the pathogenesis may differ with less evidence of antigen-driven proliferation and a greater association with direct viral infection of B cells.<sup>109,110</sup>

The strongest support for the relationship between HCV, MC, and NHL is the response to antiviral therapy. Interferon was first used to treat MC even before the discovery of HCV, with 40% to 60% of patients showing on-treatment responses; however, with this relatively ineffective antiviral regimen, relapse was common, with recurrence of MC after stopping treatment.<sup>17</sup> With the introduction of peginterferon and ribavirin, rates of SVR increased and follow-up studies showed that 80% to 90% of patients had complete resolution of MC-related complications with successful viral eradication.<sup>17,117</sup> The persistence of MC after SVR may suggest that the process has become antigen independent, with continued activity due to persistent HCV antibodies despite viral clearance or possibly due to the transformation to low-grade NHL. The introduction of DAAs holds great



**Figure 1.** HCV interactions with vascular endothelium. (A) Brain microvascular endothelial cells express all of the receptors for HCV infection and are permissive to viral replication.<sup>103</sup> Infected endothelial cells may undergo apoptosis, inducing a conformational change, allowing a breach of the blood-brain barrier. Circulating cytokines, free virus, and possibly infected peripheral blood mononuclear cells (PBMCs) may pass into the CNS, leading to microglial activation and neuronal dysfunction. (B) Cryoglobulinemia. HCV viral particles and core protein bind to marginal zone B cells. Stimulated by B cell-activating factor, released from activated dendritic cells, there is clonal expansion of B cells, leading to the release of large amounts of IgM with rheumatoid factor (RF) activity. IgM RF molecules form complexes with HCV viral particles to form cold-precipitable immune complexes, which accept the C1q protein and bind to vascular endothelial cells, stimulating the complement system, generating vasoactive peptides and the recruitment of neutrophils leading to a leukocytoclastic vasculitis. IL, interleukin; TNF, tumor necrosis factor; IFN, interferon.

promise for the treatment of MC. An initial report of treatment with peginterferon, ribavirin, and first-generation protease inhibitors in patients with MC found that all patients improved with therapy, but notably only 70% of those who achieved SVR had a complete clinical response in terms of MC-related symptoms. Even in the 10 patients who did not achieve SVR, 60% had a complete clinical response on therapy, but 2 had a subsequent recurrence of vasculitis with viral relapse.<sup>118</sup>

In patients who cannot tolerate or do not respond to antiviral therapy, immunosuppressive therapy may be required. Numerous uncontrolled studies have reported beneficial effects with glucocorticoids, azathioprine, and

other immunosuppressive regimens.<sup>17</sup> With the clear relationship between MC and B-cell populations, it was a logical step to evaluate anti-CD20 B cell-depleting agents. Rituximab has been used alone, in combination with corticosteroids, and as an adjunct to antiviral therapy.<sup>17</sup> The study designs and small sample sizes limit comparisons and strong conclusions, but most data support that rituximab is effective in the majority of patients and does not appear to negatively affect antiviral responses. For patients with severe organ- or life-threatening disease, plasmapheresis may be required along with B cell-depleting therapy. Because of its immune-stimulatory effects, interferon may exacerbate some of the symptoms of MC vasculitis, limiting the



tolerability of therapy. The introduction of interferon-free DAA regimens holds great promise for treating patients with HCV-associated MC.

Similar to MC, even low-grade NHL may respond to antiviral therapy. The first description of regression of splenic lymphoma with villous lymphocytes with anti-HCV therapy was followed by other small series documenting regression or complete remission of HCV-associated NHL with antiviral therapy in most but not all patients.<sup>119</sup> Remission of NHL has been reported in a small number of patients treated with interferon-free DAA-based regimens, suggesting that the effect is all virally mediated and not due to antiproliferative effects of interferon.<sup>120</sup> At the population level, HCV therapy has also been shown to reduce the incidence of new-onset NHL in Japan, making a case for consideration of earlier treatment, even in patients with limited liver disease, to prevent future complications.<sup>121</sup> In patients with high-grade NHL, primary treatment of the malignancy is required; however, once remission is achieved, antiviral therapy should be introduced, because SVR markedly reduces and may even eliminate the risk of relapse of NHL.<sup>122</sup> It is possible that DAA therapies could be given with or even before chemotherapy for high-grade NHL, which may improve responses and are unlikely to affect tolerability. With the remarkable progress in HCV therapy, patients with evidence of MC, even if asymptomatic, may represent a population that should be prioritized for early antiviral therapy to prevent future symptomatic vasculitis and lymphoma.

## Miscellaneous Manifestations

The array of extrahepatic manifestations associated with HCV infection is large and heterogeneous. We will discuss selected ophthalmological, mucocutaneous, and immunologic manifestations not considered in the preceding paragraphs.

### Ophthalmological

Two ophthalmological manifestations are noteworthy: Behçet disease and Mooren ulcer. In the case of Behçet disease, the causal link has never been convincingly proven,<sup>123</sup> despite initial isolated claims.<sup>124</sup> On the other hand, good evidence associates Mooren-type peripheral ulcerative keratitis with HCV, because this rare condition has been reported to improve after interferon therapy.<sup>125</sup>

### Mucocutaneous

The link between HCV and lichen planus is controversial because most studies are retrospective, making it impossible to ascertain whether HCV infection has occurred before or after the appearance of the skin lesions. In patients with oral lichen planus, HCV was shown to replicate in the oral mucosa tissue.<sup>126</sup> The affected oral mucosa may also harbor HCV-specific T lymphocytes,<sup>127</sup> underlying the pathogenetic role of HCV. However, HCV does not seem to replicate in cutaneous lichen planus tissue,<sup>128</sup> and the effect of interferon therapy in such cases has been inconsistent, thus complicating the overall picture.<sup>129</sup>

Pruritus has been reported to occur early in the natural history of hepatitis C.<sup>130</sup> Pathogenesis may involve bile duct disappearance with ensuing low-grade cholestasis.<sup>131</sup> However, in a case-control study, the prevalence of HCV was not increased among patients with pruritus, and HCV represented only a minority of the potential causal agents of chronic itching, strongly suggesting that systematic HCV screening in such cases is not indicated.<sup>132</sup>

Porphyria cutanea tarda (PCT) is the most common form of porphyria and in most cases recognizes exogenous causal agents, such as iron overload, estrogen therapy, excess alcohol consumption, and HCV infection.<sup>133</sup> HCV is a very frequent cause of PCT; according to a meta-analysis,<sup>134</sup> as many as 50% of patients with PCT may have markers of HCV infection, although a wide geographic variation in prevalence suggests that other cofactors (genetic and/or environmental) may play a role in the pathogenesis and phenotypic expression of PCT. The central pathogenetic events seem to involve iron overload and oxidative stress. Although PCT has traditionally been managed by phlebotomy, the best approach is the elimination of the causal agent. Therapy with interferon and ribavirin may exacerbate manifestations of PCT, including the appearance of blisters in sun-exposed areas, milia, hirsutism, and skin erosions. Thus, patients with PCT may particularly benefit from interferon-free regimens.

### Immunologic Disorders

One of the most intriguing and debated associations between HCV and immunologic disorders concerns rheumatoid arthritis. A recent, large, population-based cohort study assessed the risk of rheumatoid arthritis in patients with chronic infection with HCV or HBV.<sup>135</sup> A total of 35,652 patients had HBV infection alone, 10,253 had HCV infection alone, and 3987 had chronic HBV/HCV dual infections. These patients were matched with 199,568 uninfected controls and followed for a decade. After adjusting for covariates, chronic HCV infection alone was significantly associated with an increased risk of rheumatoid arthritis (HR, 2.03; 95% CI, 1.27–3.22), a risk not shared by carriers of HBV. Convincing, conclusive data on the beneficial effect of antiviral therapy (if any) are not available.

Idiopathic pulmonary fibrosis is another rare but serious condition that has been associated with HCV infection. In a large retrospective series, the incidence of pulmonary fibrosis was significantly higher among patients with HCV than HBV-infected controls.<sup>136</sup> Risk factors for the development of pulmonary fibrosis were age, smoking, and cirrhosis. This condition should not be banalized because it can be dramatically exacerbated by interferon therapy.<sup>137</sup>

Thyroid autoimmune stigmata are relatively frequent in chronic hepatitis C and may occasionally be associated with hypofunction. A genetic predisposition has been suggested, because these disorders seem to predominantly affect women with haplotype HLA DR-3.<sup>138</sup> Interferon alfa therapy can exacerbate this disorder; hyperthyroidism and hypothyroidism are equally observed in patients treated with interferon, with some experiencing permanent sequelae.

**Table 3.** Benefits Associated With Eradication of HCV Infection

Condition	Studies and main findings	Reference
Insulin resistance	Kawaguchi et al, 2007: Chronic HCV-infected patients treated with interferon alfa with or without ribavirin who achieved SVR had significantly reduced HOMA-IR values, whereas virological nonresponders and relapsers showed no change in HOMA-IR	38
	Milner et al, 2014: Patients with chronic HCV infection (n = 8) in whom HCV was eradicated after antiviral therapy had reduced peripheral insulin resistance compared with baseline; insulin sensitivity after viral eradication was comparable to that of matched uninfected controls	146
	Moucari et al, 2010: Decline in serum HCV RNA level was correlated with reduction in HOMA-IR score during 14 days of monotherapy with the NS3 inhibitor danoprevir, compared with HCV RNA level and HOMA-IR score which remained unchanged in patients receiving placebo	39
Diabetes	Arase et al, 2009: In a retrospective study, SVR after treatment with interferon or interferon plus ribavirin conferred a reduced risk (by about two-thirds) of developing type 2 diabetes mellitus, even after stratification according to age, cirrhosis, and prediabetes	143
Stroke	Hsu et al, 2013: In a retrospective cohort study, HCV-infected patients who received interferon-based therapy had a significantly reduced risk of stroke compared with untreated patients (adjusted HR, 0.39; 95% CI, 0.16–0.95)	76
Myocardial perfusion defects	Maruyama et al, 2013: Myocardial perfusion defects, found in the majority of HCV-infected patients, improved after interferon therapy in patients with SVR, did not change in nonresponders, and temporarily improved and then returned to baseline in those who experienced a relapse	75
	Cacoub et al, 2002: Achieving SVR was associated with reduction in fatigue after adjusting for age, sex, fibrosis stage, and depression (OR, 0.34; <i>P</i> < .001)	83
Fatigue and HRQOL	Hassanein et al, 2004: HCV-infected patients who achieved SVR with peginterferon plus ribavirin or interferon alfa plus ribavirin had significant improvement in HRQOL, as assessed by the SF-36 and FSS	147
	Rasenack et al, 2003: HCV-infected patients who achieved SVR after 48 weeks of peginterferon or interferon alfa therapy had significantly improved HRQOL compared with those without SVR, as measured by mean SF-36 scores and mean FSS scores	148
	Younossi et al, 2014: Patients infected with HCV genotype 2 or 3 who were treated with sofosbuvir and ribavirin and achieved SVR had significant improvements from baseline in HRQOL, as measured by fatigue, SF-36 score, emotional well-being, general health, and results of the Chronic Liver Disease Questionnaire-HCV	154
Cognitive function	Kraus et al, 2013: HCV-infected patients with SVR after treatment with peginterferon and ribavirin showed significant improvement in neurocognitive function when tested at least 1 year after the end of therapy; patients without SVR showed no changes in neurocognitive function	105
Cerebral magnetic resonance spectroscopy	Alsop et al, 2014: After treatment with ledipasvir-sofosbuvir, patients with HCV showed increases in cerebral <i>N</i> -acetylaspartate levels, interpreted as recovery of neuronal dysfunction	107
MC	Gragani et al, 2015: HCV-infected patients with MC treated with peginterferon and ribavirin showed a good clinicoimmunologic correlation with SVR, because all patients with SVR also experienced a sustained clinical response, either complete or partial, whereas all virological nonresponders were also clinical nonresponders, despite a transient improvement in some patients	117
	Saadoun et al, 2015: 30 patients with hepatitis C and MC, mostly previous nonresponders, were re-treated with peginterferon and ribavirin plus a protease inhibitor (telaprevir or boceprevir), with a high rate of both clinical and virological success despite adverse effects	118
Lymphoma	Hermine et al, 2002: In 9 patients with HCV infection treated with interferon alfa, 7 had complete remission of splenic lymphoma with villous lymphocytes on virological response, whereas the remaining 2 patients had partial and complete remission after the addition of ribavirin and disappearance of HCV RNA; 1 patient had a relapse when the HCV RNA load again became detectable after therapy	119
	Carrier et al, 2015: Five patients with HCV-associated B-cell NHL were treated with DAA (1 also received rituximab and 2 received chemotherapy in addition to DAA); SVR was reached in all, and complete remission of NHL was noted 6 months after cessation of treatment (except in 1 patient who had a persistent small leukemic phase)	120
	Kawamura et al, 2007: In a retrospective study, 501 untreated and 2708 HCV-infected patients treated with interferon were followed up to 15 years; in untreated cases, a malignant lymphoma developed in 0.6% at the 5th year, 2.3% at the 10th year, and 2.6% at the 15th year; the rates in treated patients with SVR were 0% up to the 15th year, while in those treated but not cured, the rate increased up to 2.6% at the 15th year	121
Mortality	La Mura et al, 2008: In 69 HCV-infected patients with lymphomas, antiviral therapy performed after chemotherapy (n = 25) was associated with an increased disease-free survival; none of the patients with SVR experienced a relapse of lymphoma, whereas 29% of nonresponders experienced a relapse	122
	van der Meer et al, 2012: In HCV-infected patients with advanced fibrosis or cirrhosis, achieving SVR with interferon-based therapy was associated with reduced all-cause mortality	9

FSS, Fatigue Severity Scale; SF-36, Short Form Health Survey.

Again, these patients may benefit from the advent of interferon-free regimens.

Finally, a troublesome association has been reported between HCV infection and some severe autoimmune cytopenias,<sup>139</sup> including autoimmune hemolytic anemia and autoimmune thrombocytopenic purpura. Interferon is usually contraindicated in these patients and, depending on the severity of the deficit, treatment requires use of corticosteroids, intravenous immunoglobulins, or splenectomy. In the rare cases in which interferon therapy is permitted, the cytopenia may remit. Interferon-free regimens may provide valuable treatment options for these conditions.

## Evolving Risks and Benefits of Eradication of HCV in the Era of DAAs

The availability of well-tolerated, interferon-free DAA regimens for the treatment of patients with chronic HCV infection will significantly broaden the spectrum of patients eligible for and willing to undergo anti-HCV treatment. Until recently, therapy may not have been indicated for patients at low risk for progression of liver disease due to the numerous adverse effects. In particular, immune stimulation induced by interferon has been a deterrent to the treatment of patients with hepatitis C who have various immunologic manifestations. Further, patients with comorbid conditions such as depression, cardiovascular disease, and/or severe fatigue were typically considered poor candidates for treatment with interferon alfa because this drug could worsen such conditions. The recent introduction of more tolerable, more effective therapies has significantly broadened the spectrum of HCV-infected patients who can be considered candidates for treatments aimed at eradication of HCV, including those who were interferon-ineligible or -intolerant, have a low or moderate risk of liver disease progression, or experience mainly the extrahepatic effects of HCV.<sup>22,140–142</sup>

Studies showing that successful treatment of HCV may reduce nonhepatic mortality lend credence to the concept of broader treatment indications. In a long-term study of 530 patients with advanced fibrosis or cirrhosis, SVR was associated with significantly reduced all-cause mortality.<sup>9</sup> Other studies have also shown the extrahepatic benefits of HCV eradication (Table 3); patients with SVR after peginterferon and ribavirin therapy have reduced steatosis, a lower incidence of malignant lymphoma,<sup>121</sup> reduced risk of type 2 diabetes mellitus<sup>143</sup> and insulin resistance,<sup>38,39,144–146</sup> improved cognitive performance,<sup>105</sup> reduction in fatigue,<sup>147,148</sup> improvement in myocardial perfusion defects,<sup>75</sup> reduced incidence of stroke,<sup>76</sup> reduced renal and cardiovascular outcomes in the presence of diabetes,<sup>51</sup> complete resolution of MC-related complications,<sup>17,117</sup> and regression or complete remission of HCV-associated lymphoma.<sup>119</sup> It is also clear that interferon and ribavirin-free treatment results in improved patient-reported outcomes in many patient groups after as early as 2 weeks of treatment. Clinically important gains in quality of life are associated with SVR.<sup>20,21</sup> Thus, multiple studies have shown that durable

HCV eradication achieved with interferon-based therapies improves both liver-related and non-liver-related outcomes.

The availability of safe and well-tolerated interferon-free regimens will enable the treatment of more patients, including those subgroups with immunologic and psychiatric manifestations in which interferon was generally contraindicated.<sup>149–153</sup> Indeed, clinical studies have already assessed changes in extrahepatic manifestations of HCV during treatment with new DAA regimens. For example, SVR achieved after treatment with sofosbuvir, including one interferon-free regimen, was associated with improvements in central fatigue<sup>154</sup> and in HRQOL.<sup>155</sup> Data from these studies also show that patient-reported outcomes and HRQOL are better during treatment with interferon-free DAA regimens than during treatment with interferon-containing regimens.<sup>154,155</sup> Thus, evidence is mounting that viral eradication is indeed associated with amelioration of an increasing number of extrahepatic manifestations associated with HCV, also providing, apart from a clear benefit for the patient, support for a pathogenetic link. Not surprisingly, major clinical practice guidelines of international societies have already incorporated the presence of extrahepatic manifestations (including, for example, debilitating fatigue) as a priority indication for treatment with the novel interferon-free regimens, even in the absence of significant liver damage. However, the long-term benefit of SVR in these patients, such as the prevention of NHL in patients with cryoglobulinemia, can only be proven by large prospective trials.

In conclusion, the involvement of nonhepatic organ systems in HCV infection substantially decreases the quality of life of chronically infected patients and may also increase nonhepatic mortality. Viral eradication reduces extrahepatic manifestations of HCV, and improved cure rates with new regimens will conceivably result in even more marked effects. Because these new regimens are also better tolerated than previously available treatments and have an improved risk/benefit profile, extrahepatic manifestations of HCV form an important indication for anti-HCV treatment, even in the absence of liver disease.

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Received November 15, 2014. Accepted August 17, 2015.

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#### Acknowledgments

Medical writing assistance, funded by Boehringer Ingelheim Pharma GmbH Co KG, was provided by Jennifer Tobin of Choice Healthcare Solutions.

#### Conflicts of interest

The authors disclose the following: F.N. is an advisory board member for MSD, Gilead Sciences, AbbVie, Janssen, and Bristol-Myers Squibb; has received consulting fees from MSD, Boehringer Ingelheim, and Janssen; has received grants from Roche and Gilead Sciences; and has received lecture fees from Gilead Sciences. D.F. has received consulting fees from Merck, Boehringer Ingelheim, Roche, Janssen, AbbVie, Bristol-Myers Squibb, and Gilead Sciences. A.C. is an advisory board member for and has received consulting fees and grants from MSD, Gilead Sciences, AbbVie, Boehringer Ingelheim, Janssen, Novartis, Roche, and Bristol-Myers Squibb. M.S.S. is an advisory board member for AbbVie, Achillion, Bristol-Myers Squibb, Gilead Sciences, Janssen, and Merck and has served as the principal investigator for research grants to Johns Hopkins University from AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen, and Merck. J.J.F. has served as a scientific consultant for AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck, and Theravance Biopharma and as the principal investigator for research grants to the University of Toronto from AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, Janssen, and Merck. M.P.M. has received speaker fees from AbbVie, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Janssen, Merck, and Roche; has served as a consultant for AbbVie, Achillion Pharmaceuticals, Bristol-Myers Squibb, Boehringer Ingelheim, Gilead Sciences, GlaxoSmithKline, Idenix Pharmaceuticals, Janssen, Merck, Novartis, Roche, and Vertex Pharmaceuticals; and has received grant/research support from AbbVie, Bristol-Myers Squibb, Boehringer Ingelheim, Gilead Sciences, Janssen, Merck, Novartis, and Roche.

#### Funding

Supported by Boehringer Ingelheim Pharma, GmbH & Co KG.