Chronic Hepatitis C Virus Infection and Depression

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INTRODUCTION

Chronic hepatitis C virus (HCV) infection poses a remarkable burden on the health care system worldwide because of an estimated prevalence of about 3%1 and association with significant hepatic and extrahepatic manifestations, which are still responsible for significant morbidity and mortality globally.2

Indeed, besides liver involvement (chronic hepatitis, cirrhosis, hepatocellular carcinoma), chronic HCV infection is known to be associated with a wide variety of extrahepatic manifestations,3,4 such as lymphoproliferative disorders (non-Hodgkin lymphoma and mixed cryoglobulinemia),5 cardiovascular disease (ischemic heart disease, atherosclerosis, ischemic stroke), metabolic derangements (insulin resistance and type 2 diabetes mellitus), renal involvement (membranoproliferative glomerulonephritis), autoimmune diseases (thyroiditis, sicca syndrome), and dermatologic and neuropsychiatric manifestations.6–16

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KEYWORDS

• HCV • Depression • Quality of life

KEY POINTS

• Depression is an extrahepatic manifestation of chronic hepatitis C virus (HCV) infection reported in one-third of patients.
• The prevalence of depression in patients with HCV has been estimated to be 1.5 to 4.0 times higher than that observed in the general population.
• Direct HCV neuro-invasion, induction of local and systemic inflammation, neurotransmission, and metabolic derangements are the hypothesized pathogenic mechanisms of depression.
• Depression considerably impacts health-related quality of life of HCV-positive patients.
• Clearance of HCV by antiviral treatments is associated with an improvement of both depression and quality of life.
The mechanisms by which HCV induces systemic diseases seem to be multifactorial, correlated to its ability to penetrate and replicate within cells of the main body systems and to induce local and systemic inflammation, metabolic alterations, and immune-mediated phenomena. HCV can target the central nervous system (CNS) causing a wide range of neurologic and psychiatric manifestations; indeed, more than 50% of infected individuals have been reported to have neurologic and psychiatric disorders. HCV-associated CNS conditions include cerebrovascular events (atherosclerosis, ischemic stroke), encephalic and meningeal inflammation (leukoencephalitis, transverse myelitis), vascular inflammation (vasculitis), cognitive dysfunction (inadequate concentration, physical and mental fatigue, decreased memory and psychomotor velocity), and psychiatric disorders. Among these psychiatric disorders, irrespective of antiviral treatments and alcohol and/or drug abuse, depression is the most frequent and disabling disorder, which has been reported in approximately one-third of HCV-positive patients.

The prevalence of depressive disorders seems to be significantly higher among HCV-infected patients compared with that observed in the general population using the criteria of the Diagnostic and Statistical Manual for Mental Disorders, (Fourth Edition) (DSM-IV). According to the DSM-IV, a major depressive disorder is characterized by a period of depressed mood or anhedonia (eg, inability to experience pleasure from normally pleasurable life events, such as eating, exercise, social or sexual interaction) occurring for at least 2 consecutive weeks. Depressed mood or anhedonia must also be accompanied by at least 4 of the following: (1) overwhelming sadness or emptiness; (2) lack of interest or pleasure in daily activities; (3) appetite or weight changes; (4) disturbed sleep patterns; (5) changes in psychomotor activity; (6) fatigue or loss of energy; (7) feelings of guilt or worthlessness; (8) difficulty focusing, concentrating, or making decisions; and (9) recurrent thoughts of death or suicidal ideation.

A direct or indirect effect of HCV on brain function has been hypothesized from the more pronounced metabolic cerebral alterations observed in patients with mild chronic hepatitis C as compared with healthy subjects or patients with chronic hepatitis B. Support for this hypothesis has come from the demonstration of replicative forms of HCV in the brain, implying the possibility of CNS as a favorable site for viral replication. Moreover, in chronic HCV infection, alterations in the blood-brain barrier (BBB) so as to allow the passage of circulating proinflammatory cytokines (eg, tumor necrosis factor α [TNFα], interleukin [IL]-1, IL-6), changes in neuronal metabolic pathways, and/or ischemia and vasculitis due to cryoglobulinemia all may contribute to the pathogenesis of neuropsychiatric disorders. However, it is important to underline that the mere knowledge of being HCV seropositive can reduce the sense of well-being because the fear of contagion and uncertain prognosis, social marginalization, hopelessness, and depression.

The aim of this review is to analyze the current knowledge about the relation between chronic HCV infection and depression and the possible pathogenic mechanisms as well as the effects of pharmacologic viral clearance on patients’ psychiatric features.

Hepatitis C Virus and Depression

Several psycho-diagnostic tests have been used in order to assess depression. None of these tests has been shown to possess a high diagnostic performance; however, the Beck Depression Inventory has been widely used because of superior sensibility and specificity when compared with the Hospital Anxiety and Depression Scale.
Overall, the prevalence of depression in patients with HCV has been estimated to be 1.5 to 4.0 times higher than that observed in the general population. Depressive disorders are generally associated with an impaired quality of life, a limited access to diagnostic workup and therapeutic evaluation, and a reduced adherence to treatment and follow-up.

Both depression prevalence rates and impact on quality of life seem to be unrelated to liver disease severity, preexistent psychological conditions, comorbidities, and interferon (IFN) treatment; however, because concomitant disorders and patient sociocultural background have been reported to be crucial factors or cofactors in the development of depression by some investigators, the exact role of these players is still being debated. However, the results of these later reports are controversial because of the presence of confounding bias and the small number of patients examined.

**EPIDEMIOLOGY OF DEPRESSION IN CHRONIC HEPATITIS C VIRUS–POSITIVE PATIENTS**

The earliest evidence of the role of HCV in the development of depression was provided in 1998 by Johnson and colleagues who reported a significantly higher prevalence of depressive disorders among drug users belonging to the subgroup of HCV-positive patients (57.2%) compared with HCV-negative patients (48.2%).

Using the diagnostic criteria of the *DSM-IV* for major depressive disorder, Carta and colleagues demonstrated a prevalence of 32.6%, among HCV-positive patients, a significantly higher figure when compared with that observed in healthy individuals (12.8%) and hepatitis B virus (HBV)-positive patients (15.1%). These data were, thus, suggestive for a specific role for HCV in inducing depression. Moreover, the same authors showed a significantly higher rate of recurrent brief depression (15.5%) compared with the healthy controls (6.3%). Navines and colleagues reported depressive disorders in 18.2% of HCV positive-patients, with features of a major depressive disorder in 6.4% of patients with HCV. In a group of 90 HCV-positive patients, Golden and colleagues reported a prevalence of 28% of depressive disorders with a strict correlation with psychosocial factors, such as lower acceptance of the disease and social marginalization. Similar rates of depression were reported by Dwight and colleagues, Kraus and colleagues, and Fábregas and colleagues in their patients with HCV. Recently, a large survey of US patients with HCV by Boscarino and colleagues demonstrated a prevalence of depression in 29.7% of cases. A German study showed a prevalence of depression in 25.9%. Interestingly, genotype 3a–infected patients were shown to be at higher risk of depression than those infected by genotype 1. However, because genotype 3a is known to often be associated with drug users, caution should be exercised when interpreting this finding.

Several studies emphasized the observation of significantly higher depression rates in HCV-positive (32.6%) individuals when compared with HBV-positive (15.1%) patients, possibly pointing to a specific role for HCV in the pathogenesis of depression.

In a recent meta-analysis including 130,000 patients with HCV, Younossi and colleagues reported depression rates of 24.5% and 17.2% in patients with HCV and healthy controls, respectively. Patients with HCV were found to have twice the risk of developing depressive symptoms as compared with healthy subjects. Furthermore, the risk seemed to be higher among women and to increase with age. This meta-analysis also ranked depression as the most prevalent extrahepatic manifestation of HCV chronic infection, with health care costs estimated to be around $430 million per year. Indirect costs due to lower work productivity, as highlighted by a 1.5 to 1.85 higher-than-average rate of absenteeism should also be added.
Despite consistent literature on the association between HCV and depression, the true prevalence of depressive disorders in HCV-positive patients remains an unsolved issue. Presently, the prevalence rates of depression seem to be underestimated because of several considerations: (1) screening of psychological profiles of patients with HCV is not performed routinely and often disregarded and (2) many of the aforementioned studies reported referred to tertiary center, which may limit the applicability of the data on a broad scale. In this context, Lee and colleagues evaluated a population of about 10,000 patients with chronic HCV, HBV or alcoholic hepatitis, or nonalcoholic fatty liver disease (NAFLD) sorted from the national surveillance registers of the Centers for Disease Control and Prevention. A strong correlation with depressive disorders was shown to exist only for HCV-infected subjects, thus, confirming this association on a population level as well. Nonetheless, an increased prevalence of depression was observed in patients with chronic HBV, alcoholic hepatitis, or NAFLD; however, none of these associations could be verified at the population level, unveiling a potential bias for studies including only patients referred to tertiary centers. Although the exact prevalence of depression in patients with HCV remains to be defined, most studies showed a strict association between the two conditions. The main data are reported in Table 1.

DEPRESSION AND IMPACT ON QUALITY OF LIFE AND CLINICAL MANAGEMENT OF PATIENTS WITH HEPATITIS C VIRUS

Social marginalization with difficult interpersonal relations with both familiars and non-familiars has been observed in patients with HCV with associated depression. Moreover, patients with HCV-related depression, in addition to low mood, showed loss of interest in daily activities, low self-esteem, fatigue, and a decreased capability to ideate and focus. Anxiety, insomnia, compulsivity, hypochondria, and phobias may also be present; in some cases, anger, hostility, aggressiveness, and suicidal ideation have been reported. HCV-related depression has also been associated with a lower disease acceptance, reduced working capabilities, and a high rate of somatization. In addition, patients with HCV have been found to exhibit some degree of cognitive impairment in many cases. Using the P300 evoked potential, Kramer and others showed cognitive impairment in about 17% of patients with HCV. Several studies suggest that cognitive damage may already take place in the early phases of HCV disease. Finally, when considering that patients at high risk for psychiatric disorders, such as injecting drug users, are often involved, the association between HCV chronic infection and depression gains further relevance.

Depression and associated conditions considerably impact on health-related quality of life (HRQL) of HCV-positive patients. In a recent study on blood donors, HCV-positive subjects (at first diagnosis) were found to display lower HRQL scores than HBV-positive, human T-lymphotropic virus–positive, and healthy individuals; interestingly, scores from HBV-positive donors were shown to overlap those from healthy controls. Similar results emerged from other studies, all pointing to a possible direct role of HCV in such disorders.

Depression and HCV-related fatigue have been demonstrated to be the main determinants of a low HRQL. The presence of depressive disorders was associated with a remarkable deterioration of HRQL scores and all cognitive domains. Kramer and colleagues and Hauser and colleagues provided evidence that HRQL was not influenced by liver disease severity, with the exception of decompensated cirrhosis; conversely, HRQL could be affected by the presence of a comorbidity (eg, internal and psychiatric), age, and severity of fatigue. Finally, onset of psychological disorders
Table 1

Prevalence of depression in chronic hepatitis C virus–infected patients

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Country</th>
<th>Study Type</th>
<th>HCV Patients (n)</th>
<th>Depression Prevalence in HCV (%)</th>
<th>Control Group</th>
<th>Control Patients (n)</th>
<th>Depression Prevalence in Controls (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson et al, 1998</td>
<td>United States (Alaska)</td>
<td>Observational</td>
<td>163</td>
<td>57.2</td>
<td>Drug users HCV</td>
<td>147</td>
<td>48.2</td>
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<tr>
<td>Dwight et al, 2000</td>
<td>United States (California)</td>
<td>Observational</td>
<td>50</td>
<td>28.0</td>
<td>None</td>
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<td></td>
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<tr>
<td>Kraus et al, 2000</td>
<td>Germany</td>
<td>Cross-sectional</td>
<td>113</td>
<td>22.4</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Golden et al, 2005</td>
<td>Ireland</td>
<td>Observational</td>
<td>90</td>
<td>28.1</td>
<td>None</td>
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<tr>
<td>Carta et al, 2007</td>
<td>Italy</td>
<td>Observational</td>
<td>135</td>
<td>32.6</td>
<td>CHB</td>
<td>76</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>Healthy control</td>
<td>540</td>
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</tr>
<tr>
<td>Nelligan et al, 2008</td>
<td>United States</td>
<td>Observational</td>
<td>783</td>
<td>34.0</td>
<td>None</td>
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<tr>
<td>Erim et al, 2010</td>
<td>Germany</td>
<td>Observational</td>
<td>81</td>
<td>25.9</td>
<td>None</td>
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<tr>
<td>Karaivazoglou et al, 2010</td>
<td>Greece</td>
<td>Observational</td>
<td>39</td>
<td>—</td>
<td>CHB</td>
<td>45</td>
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<td>Fabregas et al, 2012</td>
<td>Brazil</td>
<td>Observational</td>
<td>75</td>
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<td>Navinés et al, 2012</td>
<td>Spain</td>
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<td>500</td>
<td>18.2</td>
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<td>Lee et al, 2013</td>
<td>United States (Virginia)</td>
<td>Observational</td>
<td>178</td>
<td>54.6</td>
<td>CHB</td>
<td>46</td>
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<td></td>
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<td></td>
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<td>ALD</td>
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<tr>
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<td></td>
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<td>497</td>
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<td></td>
<td></td>
<td>Healthy control</td>
<td>9178</td>
<td>27.2</td>
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<tr>
<td>Boscarino et al, 2015</td>
<td>United States (Pennsylvania)</td>
<td>Observational</td>
<td>4781</td>
<td>29.7</td>
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<td>Younossi et al, 2016</td>
<td>NA</td>
<td>Meta-analysis</td>
<td>130,039</td>
<td>29.6</td>
<td>None</td>
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<td></td>
<td></td>
<td></td>
<td>24,210</td>
<td>24.5</td>
<td>HCV–</td>
<td>127,506</td>
<td>17.2</td>
</tr>
</tbody>
</table>

Abbreviations: ALD, alcoholic liver disease; CHB, chronic hepatitis B; NA, not applicable.
and a negative impact on patient quality of life were noted to merely result from a diagnosis of HCV infection as well.\(^6^4\)

On the other hand, early diagnosis and treatment of depression were shown to have a positive impact on HRQL.\(^6^5\) Moreover, antiviral treatment-induced HCV eradication was associated with an improvement in quality of life,\(^6^6\) further supporting a pathogenic role for HCV.

The presence of depression has long been regarded as a substantial barrier to treatment adherence in cases of IFN-based regimens.\(^6^7,6^8\) A history of depression is indeed a significant risk factor for new development of depression during IFN treatment.\(^6^9\) Specifically, moderate to severe depressive symptoms have been described as side effects of IFN-based regimens in about 40% of HCV-infected patients.\(^7^0\)

### MECHANISMS INVOLVED IN HEPATITIS C VIRUS–ASSOCIATED DEPRESSION

The mechanisms by which HCV could be involved in the development of depression and other neuropsychiatric conditions are as yet unclear. Although psychosocial factors (eg, intravenous drug use, alcohol, female gender) may be significantly involved, hint at a possible role of HCV have emerged from several studies. Direct HCV neuroinvasion, induction of local and systemic inflammation, neurotransmission, and metabolic derangements are among the pathogenic mechanisms thus far hypothesized.

A direct effect of HCV on the CNS was proposed more than 15 years ago as a mechanism for the neurocognitive impairment reported in this infection.\(^2^6\) Apart from the known ability to replicate in different anatomic sites (eg, lymphoid organs, bone marrow, pancreas, thyroid, spleen) and cells (T cells, B cells, macrophages, endothelial cells),\(^1^7,7^1–7^3\) HCV has also been deemed to have a permissive site for replication in the CNS;\(^2^3,7^4–7^8\) owing to the detection of a negative-strand of HCV RNA sequences, that is, intermediate replicative forms of viral genome, in the brain.\(^7^4,7^9\)

With regard to mechanisms of viral entry in the CNS, HCV has been theorized to access the brain via the cerebrospinal fluid or, more likely, endowed in infected monocytes/macrophages, thereby crossing the BBB by means of a so-called Trojan horse mechanism.\(^7^5\) Once in the brain, the colonization of resident microglial cells may take place; their subsequent activation would involve several metabolic changes.\(^3^2\) Indeed, findings from studies with proton magnetic resonance spectroscopy (MRS), which provides information on cerebral metabolism, pointed to microglial cells as HCV host cells in the brain.\(^2^6,3^2\) Regardless of hepatic encephalopathy and substance abuse, an increase in the choline/creatine ratio\(^2^6\) and a reduction in the levels of N-acetyl aspartate\(^8^0\) were observed in the white matter and in the basal ganglia of HCV-positive patients as compared with either HBV-positive individuals or healthy controls. Using PET, activation of microglial cells in HCV-affected patients has been recently demonstrated, with a positive correlation with viremia and alterations in cerebral metabolism.\(^8^1\) Assessment of activation in macrophagic/microglial cells in HCV-positive patients was carried out by Wilkinson and colleagues,\(^8^2\) who documented increased gene transcription for the proinflammatory cytokines TNF-\(\alpha\), IL-1\(\beta\), and IL-6. As previously shown for human immunodeficiency virus (HIV),\(^8^3\) TNF-\(\alpha\) is known to exert a direct neurotoxic effect, whereas IL-1\(\beta\) neurotoxic effects are mediated by the inducible nitric oxide synthase into the astrocytes.\(^8^4\) Moreover, an altered BBB integrity and efficiency may favor the access of cytokines, pathogens, or immune cells in the CNS, which all may contribute to the genesis of neuropsychiatric manifestations during chronic HCV infection.\(^8^5\) Fletcher and colleagues\(^7^7\) have recently located the access site of HCV in the CNS in the BBB endothelial cells. Accordingly, these cells have been found to express the main viral receptors, such
as low-density lipoprotein receptor, tetraspanin CD81, scavenger receptor BI, and tight junction proteins claudin-1 and occludin.\(^\text{86,87}\) Besides, neuroepithelioma-derived cell lines have been demonstrated to express functional receptors allowing HCV entry, thus, supporting the notion of HCV infecting CNS cells in vivo.\(^\text{88}\)

Different HCV strains have been speculated to display a different cellular tropism on discovery of different HCV strains in diverse anatomic sites in the same subject.\(^\text{74}\) Forton and colleagues\(^\text{75}\) hypothesized that polymorphisms in the internal ribosomal entry site regions of the HCV genome may lead to a decreased synthesis of viral proteins in microglial cells, thus, reducing the chances of immune-mediated recognition and elimination of infected cells. As a result, HCV may persist in the brain; this mechanism would explain its neurotropism.

Besides neuro-invasion, HCV-induced chronic inflammation state may contribute to explain the pathogenesis of neurologic damage.\(^\text{91}\) A crosstalk between inflammatory pathways and neuro-circuits in the brain has been determined to underlie behavior response, particularly development of depression.\(^\text{89}\) As mentioned earlier, proinflammatory cytokines (TNF\(\alpha\), IL-1, IL-6) produced in situ by cerebral microglial cells or landed into the CNS through a BBB made permeable by the virus have been shown to exert a neurotoxic effect and to modulate cerebral activity. Huckans and colleagues\(^\text{90}\) expanded this concept by stressing the role of systemic inflammation, in addition to cerebral inflammation, in the development of neuropsychiatric disorders. Indeed, they reported elevated inflammatory signatures in HCV-positive patients, significantly related to the severity of depression and mood disorders. Likewise, Loftis and colleagues\(^\text{91}\) detected higher TNF\(\alpha\) plasma levels in HCV-positive patients with respect to seronegative controls; moreover, a direct correlation between depressive symptoms and levels of TNF\(\alpha\) and IL-1\(\beta\) was observed, thus, stressing the tight correlation between the severity of depression and the expression of proinflammatory cytokines in patients with HCV.

Several conditions whose hallmark is a strong immune activation has been associated with depressive disorders.\(^\text{92}\) In these settings, the chances for mood disorders to manifest would depend on the extent of the contrasting effects on serotonergic activity exerted by immune activation.\(^\text{93}\) Based on these observations, some investigators link the genesis of depressive symptoms in patients with HCV to the virus’ ability to generate a state of immune hyperactivation, as opposed to what is commonly observed in HBV infection, which is associated with less psychological deterioration.\(^\text{43}\)

Evidence is accumulating that cytokines can interfere with dopaminergic pathways, resulting in a state of decreased motivation or anhedonia, a core symptom of depression.\(^\text{89}\) Actually, by means of single-photon emission computerized tomography, alterations in dopaminergic and serotonergic neurotransmission have been observed in 50% and 60% of patients with HCV, respectively.\(^\text{94}\) Of note, these alterations have been found to correlate with cognitive impairment. Consistently, Heeren and colleagues\(^\text{95}\) reported significantly reduced levels of striatal and mesencephalic dopamine and glucose metabolism in the limbic area in a cohort of patients with HCV with cognition and mood alterations, thus, supporting the notion that metabolism and cerebral neurotransmission changes may underline neuropsychiatric manifestations in patients with HCV. Moreover, a strict relation between reduced serum levels of tryptophan (precursor of serotonin) and the incidence of depression and anxiety in patients with HCV has been observed;\(^\text{96}\) on the contrary, patients with HBV and healthy volunteers failed to display such an association. The development of depression may be aided by an increased platelet serotonin transporter activity, which results in reduced serotonin levels in the intersynaptic space.\(^\text{97}\)
Recently, perfusion-weighted MRI allowed to detect concomitant hypoperfusion of several cortical systems (particularly, frontal and temporoparietal cortex) as opposed to hyperperfusion, due to hypermetabolism, in the basal ganglia of patients with HCV. These findings were interpreted as possible signs of inflammation in the early stages of cerebral damage during the course of viral neuro-invasion.

Novel molecular pathways, potentially involved in the pathogenesis of depressive disorders, are being characterized. A possible role for brain-derived neurotrophic factor, a growth factor involved in neural development and regeneration, has been proposed because of remarkably low levels of this molecule in patients with HCV as opposed to patients with HBV. However, study limitations due to the small number of patients and the presence of confounding factors preclude drawing definitive conclusions.

Sheridan and colleagues focused on the role of apolipoprotein E for its role in maintaining BBB integrity and correct neuronal signaling. Patients with HCV with depression were shown to exhibit lower levels of apolipoprotein E and cholesterol than patients with no psychiatric symptoms. Hence, the investigators suggested that apolipoprotein E deficiency might alter BBB permeability by weakening the tight junctions among adjacent endothelial cells, thus, favoring HCV entry in the CNS. Furthermore, apolipoprotein E receptors were found to interact with N-methyl-D-aspartate receptors, which are involved in brain dopaminergic pathways. This finding provides further evidence of the role of apolipoprotein E in the pathogenesis of HCV-related psychiatric disorders.

Many patients with HCV have been found to have reduced levels of adiponectin. There is evidence on a possible role of low serum adiponectin levels in the pathogenesis of psychiatric disorders. Consequently, adiponectin has been suggested to exert a protective role in the development of depression in HCV infection.

In the past, an additional role was also played by IFN-based treatments, which were known to be able to induce depression, suicidal ideation, and several psychiatric symptoms. The incidence of depression during IFN treatment ranged between 17% and 44%, depending on which study is being taken into account. History of psychiatric disorders, female sex, patient sociocultural level, drug dosage, and treatment duration were identified as predictive factors for the development of depression during IFN therapy. Other than impairing quality of life, adherence to treatment itself was negatively affected, with a resulting limitation of its efficacy. Potentially involved pathogenic mechanisms included neuroendocrine and neurotransmitter alterations, particularly within serotonergic circuits, as IFN was known to lead to reduced synaptic concentrations of serotonin. Further pathogenic mechanisms of IFN-induced depression have been linked to excessive responses from the hypothalamus-hypophysis-adrenergic axis and alterations in brain cytokine pathways. In this regard, significant TGFβ1 downregulation and secondary changes in the balance of Th1/Th2 cytokines have been shown to correlate with IFN-induced depression.

**THERAPEUTIC APPROACHES**

Depression and HCV-related fatigue are the main crucial determiners of a low HRQL. Early and adequate management of HCV-associated depression positively affects patients’ quality of life. Because IFN is deemed to induce depression by decreasing synaptic concentrations of serotonin, drugs of choice are, hence, selective serotonin reuptake inhibitors. Moreover, such drugs have been successfully used both for treatment of HCV-related depression.
and prevention and treatment of IFN-related depression.\textsuperscript{116} However, when starting antidepressant therapy, drug-drug interactions, baseline hepatic function, drug potential for hepatotoxicity, and other likely adverse side effects should be thoroughly taken into account. Nevertheless, if we assume that chronic HCV infection plays a role in the development of depression, an etiologic therapy would be regarded as the best therapeutic approach. After being the gold standard of HCV treatment for nearly 25 years, IFN and ribavirin have now been replaced by all-oral IFN-free regimens. Second-generation direct-acting antivirals (DAAs) currently enable a sustained virologic response (SVR) in more than 90\% of cases.

Depression was an important limitation to the use of an IFN-based regimen.\textsuperscript{55,117–119} Nonetheless, despite the possibility of worsening quality of life and depression during an IFN-based treatment,\textsuperscript{120} patients who achieve SVR benefitted from a significant improvement in HRQL score,\textsuperscript{117,120,121} perceived well-being, and functional state.\textsuperscript{66} Moreover, patients with HCV who responded to treatment displayed a reduced choline/creatine ratio in the basal ganglia\textsuperscript{26} on MRS, whereas nonresponders and relapsers consistently exhibited a high ratio.\textsuperscript{122} These findings were in line with an improvement in cerebral metabolic pathways following HCV clearance. A recent review confirmed the beneficial effects of SVR on HRQL and mental health outcomes, which remained compromised in those failing an SVR.\textsuperscript{123}

In 2011, first-generation DAAs, telaprevir and boceprevir, were added to IFN and ribavirin in the treatment of HCV. SVR rates were increased but at the cost of significant side effects. Again, despite limitations in use and worsening quality of life during treatment, patients achieving an SVR, nonetheless, obtained a significant improvement of HRQL.\textsuperscript{124}

In the last years, second-generation DAAs have become available and are now the gold standard of HCV treatment. These drugs have allowed more than 90\% SVR, with an excellent safety profile; when compared with IFN-based regimes, second-generation DAAs are less likely to negatively impact on patients’ quality of life during the treatment.\textsuperscript{125} Because of their recent introduction, data on the effect of new DAAs on depression are scant, even though depressive disorders and quality of life seem to improve following an SVR of the subjects who achieved SVR.\textsuperscript{125–135} Regardless of the degree of hepatic fibrosis, patients with HCV who achieve an SVR with ledipasvir/sofosbuvir have been shown to exhibit improved quality of life, working productivity, and fatigue.\textsuperscript{127,136} Because such improvements occurred early following viral clearance, a pathogenic role for HCV rather than the liver damage was hypothesized. Similar results have been reported for sofosbuvir and ribavirin\textsuperscript{127} and for the sofosbuvir and velpatasvir combination.\textsuperscript{133} Positive results have also been observed in cirrhotic patients\textsuperscript{132} and HIV/HCV-coinfected patients.\textsuperscript{129} Overall, these preliminary data seem to suggest that viral eradication, independently of the drug used, is of utmost importance to improve patients’ quality of life, although caution is necessary because HRQL might be somehow influenced by patients’ awareness of treatment success. In addition, viral clearance results in reduced absenteeism from work and increased productive capacity. Younossi and colleagues estimated an annual social cost of $7.1 billion in the United States in case no patients affected by HCV genotype 1 chronic infection were treated. On the other hand, should all the affected patients be treated, an annual net profit of $2.7 billion (taking only genotype 1 into consideration) would result. This prediction may as well be applicable to Europe and Asia.\textsuperscript{131}

**SUMMARY AND PERSPECTIVES**

Depression is a frequent extrahepatic manifestation of HCV chronic infection,\textsuperscript{16} with a significant impact on patients’ quality of life. Although HCV seems to play a role in the
pathogenesis of depression, as inferred by many studies on this topic, there is still much to be elucidated, in terms of both prevalence rate and pathogenic mechanisms. Diagnosis of depression must be made as soon as possible, because adequate management results in improved quality of life. Etiologic treatment of HCV-associated depression would be desirable; however, data on new DAAs’ efficacy are currently lacking and eagerly awaited. Now that safe and effective all-oral IFN-free regimens have become available, the relationship between HCV infection and neuropsychiatric conditions can be better investigated; a quick improvement in psychiatric symptoms would be expected if, as correctly hypothesized, they are attributable to HCV itself. The current high cost of the new all-oral regimen allows access to treatment only for a restricted number of HCV-infected patients; at present, many countries have chosen to treat only patients with advanced liver disease. However, this strategy does not take into account the systemic effects of chronic HCV infection, including such a remarkable manifestation as depression. Moreover, it has been reported that patients with HCV under a watchful waiting strategy, for whom the treatment with DAAs has been delayed, might be at a higher risk of developing depression. Thus, a global effort is urgently needed to grant patients large-scale access to all-oral anti-HCV regimens.

REFERENCES


