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**Alcoholic liver disease and hepatitis C virus infection**

Novo-Veleiro I *et al.* Alcohol and HCV infection

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**Abstract:**

Alcohol consumption and hepatitis C virus (HCV) infection have a synergic hepatotoxic effect, and the coexistence of these factors increases the risk of advanced liver disease. The main mechanisms of this effect are increased viral replication and altered immune response, although genetic predisposition may also play an important role. Traditionally, HCV prevalence has been considered to be higher (up to 50%) in alcoholic patients than in the general population. However, the presence of advanced alcoholic liver disease (ALD) or intravenous drug use (IDU) may have confounded the results of previous studies, and the real prevalence of HCV infection in alcoholic patients without ALD or prior IDU has been shown to be lower. Due to the toxic combined effect of HCV and alcohol, patients with HCV infection should be screened for excessive ethanol intake. Patients starting treatment for HCV infection should be specifically advised to stop or reduce alcohol consumption because of its potential impact on treatment efficacy and adherence and may benefit from additional support during antiviral therapy. This recommendation might be extended to all currently recommended drugs for HCV treatment. Patients with alcohol dependence and HCV infection, can be treated with acamprosate, nalmefene, topiramate, and disulfiram, although baclofen is the only drug specifically tested for this purpose in patients with ALD and/or HCV infection.

**Key words:** Alcohol use disorder; Alcohol dependence; Alcoholism; Alcoholic liver disease; Hepatitis C virus infection; Hepatitis C virus infection treatment

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**Core tip:** Alcohol favors hepatitis C virus (HCV) replication and diminishes immune response against it, increasing the risk of advanced liver disease. HCV infection prevalence among alcoholics, initially thought to be much higher (up to 50%) than in the general population, has been reported to be lower in recent studies. Intravenous drug use and advanced alcoholic liver disease may confound the prevalence of HCV infection among alcoholics. Before starting HCV infection treatment, patients should be screened for alcohol use disorder and abstinence should be achieved. Baclofen may be the drug of choice for patients with alcohol dependence and advanced liver disease.

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**INTRODUCTION**

The relationship between alcohol consumption and hepatitis C virus (HCV) infection has been a high-activity focus of investigation for decades[1–3]. The first studies addressing this association, published in the early 1990s, showed an increased prevalence of HCV antibodies in alcoholic patients, with up to 30%–40% prevalence of chronic HCV infection reported in this population[4]. These high figures decreased in subsequent years[5–7], and our research group has documented an estimated average weighted prevalence of HCV infection of 16.32% among alcoholics, after a systematic review on this topic[8]. Nevertheless, this prevalence is much higher than in the general population, reported to be about 1.5%–2%[9,10].

Although HCV prevalence is expected to decrease dramatically due to the availability of new treatments[11], the association of HCV with alcohol consumption still represents a problem of great relevance. Furthermore, complex interactions between these factors pose a challenge to physicians. In patients with chronic HCV infection, alcohol consumption is a well-known risk factor for progression to advanced forms of liver disease and cirrhosis[12]; it also increases the risk of developing hepatocellular carcinoma (HCC)[13]. Indeed, HCV infection and alcoholic liver disease (ALD) are the two main causes of liver transplantation in developed countries, and the coexistence of these diagnoses is linked to 10%–14% of cirrhosis cases and 8–10% of liver transplants in the United States[14].

The deleterious effects of this association may extend beyond ALD-specific outcomes. In patients with chronic HCV infection, alcohol consumption significantly reduces survival time, with a stronger effect in females[15]. In addition, alcoholic patients with HCV infection have been reported to have a two- to eight-fold increased risk of all-cause mortality compared with those without this infection[16,17].

**INTERACTION BETWEEN ALCOHOL AND HCV**

The development of *in vivo* models to study the pathophysiological mechanisms underlying the interaction between alcohol consumption and HCV infection represents a major challenge because of methodological and technical problems. Thus, although a synergic hepatotoxic effect appears to explain the negative consequences of the interaction between alcohol and HCV in the liver[18], the exact mechanisms of this interaction remain incompletely understood. The amount of alcohol consumption necessary to increase the risk of ALD in patients with HCV infection also remains unknown. Some studies have found that 30–40 g alcohol per day increased the risk of liver disease progression[19,20], but other authors have suggested that larger amounts (~80–120 g/day) are necessary to produce this effect[21,22]. In any case, many studies have analyzed potential mechanisms of liver damage by the combined effects of HCV and alcohol, which may be summarized as follows.

***Altered cell-mediated immunity***

Several studies have demonstrated that both alcohol and HCV can alter the differentiation and function of host dendritic cells[23–25]. Alcohol modifies the antigen-presenting function and diminishes the host response to viral peptides in hepatic cells, such as NS5 protein. Alcohol consumption may thus favor HCV evasion from immune response[25].

***Increased oxidative stress***

Chronic ethanol intake increases oxidative stress through several pathways. For instance, alcohol up-regulates the expression of cyclooxygenase 2 (COX-2), which is closely related to augmented oxidative stress and free oxygen radical production[26]. HCV also increases COX-2 expression; thus, this common pathway can amplify liver damage. Furthermore, toxic effects of alcohol on mitochondrial function may inhibit cellular regeneration in the liver[27,28], and HCV core proteins can also cause mitochondrial damage through free oxygen radical generation[29]. In line with these hypotheses, animal models have shown that alcohol-fed mice with deficient antioxidant function developed more severe forms of ALD[30]. Recently, concomitant alcohol consumption and HCV infection have been found to induce post-transcriptional modification of the expression of FOXO3, a component of the hepatic antioxidant system, leading to altered antioxidant function and potential out-of-control cell proliferation[31].

***Increased* *viral replication***

Some *in vitro* hepatocyte studies have demonstrated an increase in HCV replication with alcohol exposure[32,33], although this effect has not been demonstrated clearly in humans. Indeed, a meta-analysis performed in 2005 reported no increase in HCV RNA levels in the blood of patients with chronic alcohol consumption[34]. Recent evidence has suggested that miR-122 facilitates the replication of HCV and that alcohol induces up-regulation of this micro-RNA, thereby promoting HCV replication[35,36]. These observations highlight the potential relevance of micro-RNA in alcohol-induced organ damage, which has been described recently[37–39].

***Quasi-species generation***

Free oxygen radicals induce viral genome mutations, and alcoholic patients had been shown to have greater quasi-species complexity than do non-alcoholic controls[40,41]. Although the clinical relevance of this finding is unclear, it could reduce the response to HCV treatment.

***Liver steatosis***

Most heavy drinkers develop liver steatosis[42] and it is also known that HCV infection is associated with liver steatosis[43]. Further, non-alcoholic fatty liver disease is the main cause of chronic liver disease in developed countries[44]. The concomitant presence of ethanol, HCV infection and steatosis is associated with liver fibrosis and is able to accelerate the development of advanced liver damage[20,45].

***Iron accumulation***

Liver iron is increased in patients with ALD and, to a lesser extent, in patients with HCV chronic infection[46,47]. Iron overload is associated with increased liver inflammatory response due to the production of reactive oxygen species and may impair immune response against HCV virus infection. Therefore, it is a key mechanism of liver injury among patients with HCV infection and excessive ethanol consumption[48].

**GENETIC FACTORS ASSOCIATED WITH PROGRESSION OF LIVER DISEASE IN PATIENTS WITH ALCOHOLISM AND HCV INFECTION**

The susceptibility to advanced liver disease due to ethanol intake[49] or HCV infection[50] is known to be influenced by genetic factors. The identification of genetic variants associated with the development of liver disease due to the combined effects of ethanol and HCV would thus be of interest, as it could provide insight into the pathophysiology of alcohol–HCV interaction and help to identify high-risk patients. Regrettably, very few studies have been performed in patients with liver disease due to both excessive alcohol consumption and HCV infection[51,52], and data are insufficient to draw definite conclusions. Nonetheless, many studies have separately analyzed genetic susceptibility to these two forms of liver disease, and their findings enable the identification of common genetic factors involved in liver disease progression due to alcohol or HCV.

In this regard, many allelic variants, including single nucleotide polymorphisms (SNPs), have been analyzed, but only one genetic variant has been shown to clearly influence the risk of both ALD and HCV-induced liver damage. Namely, the rs738409 SNP in the adiponutrin or patatin-like phospholipase domain containing 3 (PNPLA3) gene has been associated in several meta-analyses with ALD[53], fibrosis progression in HCV-infected patients[54], and HCC in patients with cirrhosis due to HCV infection and/or alcohol consumption[55].

Some researchers have suggested, however, that the association of this SNP with HCV-related liver fibrosis is due to confounding factors, such as ethanol intake among HCV-infected patients[54]. This hypothesis stems mainly from the lack of biological plausibility of the association between this polymorphism and HCV infection, and the findings of one study showing that the relationship of this polymorphism to HCV-related liver disease was present only in patients with significant ethanol consumption[56]. This study has not been replicated, and a large body of evidence identifies this genetic variant as a risk factor for advanced liver disease due to many causes, including not only ethanol and HCV infection, but also non-alcoholic fatty liver disease and hepatitis B virus infection[53,54,57,58]. Furthermore, although the functional role of this polymorphism was initially described as involvement in lipid metabolism, this genetic variant may also directly influence inflammation and fibrogenesis[59,60]. Thus, it is very likely to be a common factor for liver injury.

Allelic variants in glutathione S-transferase (GST) detoxification enzymes may also be associated with susceptibility to liver disease due to ethanol and HCV infection. Specifically, null variants of *GSTM1* and *GSTT1* have been associated with the development of HCC in HCV-infected patients[61–63], and alcoholic patients carrying the *GSTM1* null, but not the *GSTT1*,genetic variant have an increased risk of ALD[64]. Although the strength of evidence from candidate gene association studies is weak to moderate, we have to consider that this relationship is biologically plausible due to the role of GST enzymes in liver disease.

The roles of inflammation-related genes in ALD and HCV-related liver injury have been extensively studied, but discordant results have been reported. An association was found between the -592C/A interleukin (IL)-10 gene polymorphism and liver cirrhosis in HCV infected patients[65], but this SNP was not related to the risk of ALD[66]. Similarly, the -174 G/C IL-6 polymorphism was associated with liver cirrhosis and HCC in HCV-infected patients[67], but not in alcoholic patients[68]. On the other hand, allelic variants -238G/A and -308G/A within the tumor necrosis factor-alpha gene (*TNFA*) may be significant predictors of HCC in HCV-infected patients[69–72], and the A allele of the -238G/A SNP of this gene was also associated with ALD in a meta-analysis[73].

In summary, strong evidence supports the association of the rs738409 SNP in the PNPLA3 gene with both ALD and HCV-related advanced liver disease. Evidence for the associations of other genetic variants, such as *GSTM1* *null* and *TNFA* -238G/A, is weak or moderate.

**HCV INFECTION PREVALENCE AMONG ALCOHOLIC PATIENTS**

The prevalence of HCV infection has traditionally been assumed to be much higher in alcoholic patients than in the general population, which is estimated around 0.5%–2% in developed countries[74]. The reported prevalence of HCV infection in alcoholic patients is very high, but variable (ranging from 2.1%[75] to 51%[76]). This variability may be related to differences in the distribution of risk factors for HCV infection among study populations[77–79].

In an attempt to integrate the findings of these studies, we recently carried out a systematic review of previous literature, including data from our own series. After combining data from 25 studies that reported the prevalence of chronic HCV infection in alcoholic patients[8], we found an average weighted prevalence of 16.32%[8]. Of interest, however, the average prevalence was much lower in alcoholic patients without that in those with prior intravenous drug use (IDU; 6.6% *vs* 72.8%)[8]. We also found relevant differences in HCV infection prevalence between patients with severe forms of liver disease (32.9%)[8] and those without liver disease or with only steatosis (5.9%). Indeed, the overall prevalence of HCV in our series (3.5%), which included small numbers of patients with IDU and/or ALD, was lower than reported in most previous studies[8], and was similar to that described in a recent paper (5.2%)[80]. Apart from a potential decrease in HCV prevalence in the general population during the last decade[81], these low prevalence rates observed in recent studies may be caused by the current low prevalence of IDU among alcoholic patients in developed countries (2.3% in our series)[8]. Furthermore, advanced ALD and IDU may confound the real prevalence of HCV infection in alcoholic patients.

Indeed, many previous studies of HCV prevalence among alcoholics included large numbers of patients with advanced forms of ALD[1,77,79] or even restricted inclusion to patients with liver disease[4,82–85], which could be considered selection bias. As HCV infection is a risk factor for the development of liver disease, alcoholics with liver disease are more likely to have HCV infection. Accordingly, these patients are more likely to be tested for HCV infection, favoring their inclusion in cohort studies. On the other side, alcoholic patients showing minor or no alteration of liver function, who are less likely to be HCV infected, may be under-represented in most studies. The situation is similar for IDU, as many studies have included large proportions of patients with this risk factor, whose presence could be considered a confounding factor of HCV infection prevalence among alcoholic patients[1,6,7]. In our series, the prevalence of HCV infection among alcoholics without ALD or IDU was only 1.1%, similar to that in the general population in Spain (1%–2.6%)[9]. In light of these data, the high prevalence of chronic HCV infection among alcoholics appears to be restricted to those with liver disease and/or IDU. Although alcohol intake may promote some risk behaviors for HCV infection, this association is controversial and evidence for ethanol as a risk factor for HCV infection *per se* is lacking[86–88].

**MANAGEMENT OF HCV INFECTION IN ALCOHOLIC PATIENTS**

***Testing***

Whether all alcoholic patients, or only those with risk factors (such as IDU), should be screened for HCV remains unclear. Current European Association for the Study of the Liver (EASL) guidelines and recommendations advise HCV testing in patients with proven ALD[89] or persistent abnormal alanine aminotransferase levels[90], but no specific recommendations have been provided for alcoholic patients without ALD. Centers for Disease Control and Prevention guidelines[90] do not include alcoholism as a risk factor for HCV infection (HIV infection and IDU are included), but many patients with past or present histories of heavy alcohol intake should likely be tested, in light of current recommendations for testing of all adults born between 1945 and 1965[90].

***Assessment of liver disease***

Liver biopsy is the gold standard for assessing liver disease severity in both ALD and HCV chronic infection, which is of particular relevance for the choice and timing of antiviral therapy[89,91]. Liver biopsy, however, is associated with significant morbidity, and several non-invasive methods have been developed that can be used to assess liver disease severity, including liver stiffness measurement and panels of biomarkers of fibrosis (scores like Hepascore®, Fibrometer®, or Fibrotest®)[92]. Therefore, liver biopsy it is not recommended in all patients with suspected liver disease due to ethanol and/or HCV infection. Although the indications of this technique are not clearly established, it may be required in patients with contradictory results after assessment with non-invasive markers or with other confirmed or suspected risk factors (such as obesity, iron overload, or even surreptitious alcohol use), which could influence the development of liver disease. It is indicated in patients with suspected aggressive forms of liver disease, like acute alcoholic hepatitis, which could benefit from specific treatments, and it is recommended in the setting of clinical trials[89].

The remainder of patients, especially those with high risk of complications from liver biopsy, could be correctly diagnosed by clinical, biochemical and radiological data. In this setting, liver stiffness measurement by elastography, alone or in combination with other methods, can safely provide enough information about the grade of liver fibrosis in patients with liver disease due to HCV infection and alcoholism[93].

***Treatment***

HCV infection treatment in alcoholic patients presents a challenge, as most studies testing the efficacy of new drugs for HCV infection have excluded these patients. EASL guidelines published in April 2014 included mention of possible first-line treatment drugs such as daclatasvir, sofosbuvir, and simeprevir, in addition to or in combination with interferon and ribavirin, for HCV genotype 1–infected patients[91]. However, exclusion criteria of clinical trials that supported the use of these new drugs included chronic liver disease other than HCV infection[94–96]. Furthermore, none of these studies specified the level of participants’ alcohol consumption[94–96]. The situation is similar for sofosbuvir and ribavirin regimens for patients infected by other genotypes, since there are no data regarding alcohol consumption to make specific recommendations[97–99].

American Association for the Study of Liver Diseases guidelines published in January 2015 recommend ledipasvir/sofosbuvir, paritaprevir/ritonavir/ombitasvir plus dasabuvir, or sofosbuvir/simeprevir with or without ribavirin as the only three valid regimens for genotype 1 HCV infection treatment[100]. The efficacy of the new combination of ledipasvir and sofosbuvir was demonstrated in a recent study, which did not use alcohol consumption as an exclusion criterion, but data regarding alcohol intake were not reported[101,102]. The pivotal study examining the new combination of paritaprevir/ritonavir/ombitasvir plus dasabuvir, not yet approved in Europe, excluded patients with recent histories of drug or alcohol abuse or positive screening results for drug or alcohol use[103]. Therefore, very little data regarding HCV treatment with new drugs among patients with alcohol consumption is available.

Previous studies, however, show that alcohol consumption is associated with a poorer response to the classical treatment of interferon and ribavirin[104], and heavy drinkers had a reduced sustained viral response (SVR) in comparison with moderate drinkers. In a Swiss cohort, SVRs were similar in patients who consumed ≤ 24 g/d alcohol during therapy and those who abstained[105]. Alcohol is known to interfere with the action of interferon[106], and poor adherence to treatment in alcoholic patients could play an important role in the efficacy of ribavirin as well[104]. Of note, SVR rates are similar in alcoholic patients who achieve abstinence and non-alcoholics[107]. In any case, no ethanol consumption threshold guiding the non-initiation of HCV treatment with interferon and ribavirin or the selection of a different treatment scheme has been established[104]. Accordingly, current EASL guidelines do not recommend a minimum abstinence period before starting treatment for HCV infection in alcoholic patients, but insist on the need to achieve abstinence before treatment[91].

Finally, previous HCV treatment guidelines recommended telaprevir and boceprevir as useful second-line drugs in combination with classical treatment; however, current EASL guidelines recommend the use of these drugs only as a last alternative when other combinations have failed[91]. No recommendation for boceprevir and telaprevir use has been provided specifically for alcoholic patients[108–111].

In summary, evidence on HCV treatment with newer drugs in alcoholics is lacking compared with interferon and ribavirin treatment. Regardless of the drug used, patients should be advised to stop or reduce alcohol consumption before starting treatment because of the potential impacts on treatment efficacy and adherence. HCV treatment for patients who cannot abstain completely from alcohol should be individualized, with consideration of their ability to adhere to medication regimens. Patients with ongoing alcohol consumption during HCV treatment may benefit from additional support in order to achieve abstinence and should be advised about potential interactions[91].

**MANAGEMENT OF ALCOHOL USE DISORDERS IN PATIENTS WITH HCV INFECTION**

The most recent version of the Diagnostic and Statistical Manual of Mental Disorders groups the diagnoses of alcoholic abuse and dependence under a new term: alcohol use disorder (AUD)[112]. The coexistence of HCV infection and AUD may be common in patients with liver damage, as explained previously[113]. Thus, assessment of alcohol consumption in HCV-infected patients is of great relevance, due to the interaction between these factors and availability of various screening tools to detect excessive alcohol intake. The widely used Alcohol Use Disorders Inventory Test (AUDIT) has been validated in several medical settings[114] and applied to HCV-infected patients[115]; it could thus be recommended in this setting. However, World Health Organization (WHO) recommendations for the care of people infected with HCV[116] suggest the use of the Alcohol, Smoking and Substance Involvement Screening Test[117]. In any case, the detection of excessive ethanol intake or at-risk drinking should prompt evaluation of patients for the presence of AUDs. Apart from clinical suspicion and screening tools, biological markers of excessive alcohol intake, such as gamma-glutamyltransferase and aspartate aminotransferase, may be useful for the identification of heavy drinkers, although the specificity of these tests is lower in this setting due to HCV-induced liver damage. Increased mean corpuscular volume and/or elevated serum carbohydrate-deficient transferrin concentration may play a more relevant role in the suspicion of AUD or heavy ethanol intake in HCV-infected patients[113].

Once heavy drinking and/or AUD are diagnosed, treatment of these disorders in patients with HCV infection should not be delayed. For patients with heavy ethanol intake but no diagnosis of AUD, the WHO and other guidelines recommend a brief intervention or the use of self-help guides immediately after detection of risky alcohol consumption[118,119]. Patients with AUD may require specialized treatment for alcoholic dependence, including specific drug treatment and/or psychosocial intervention. Many clinical tools are available for psychosocial intervention, such as the Twelve-Step Facilitation Therapy, motivational enhancement therapy, cognitive-behavioral therapy, and mutual help groups and associations such as Alcoholics Anonymous[113].

Regarding pharmacologic treatment, a recent meta-analysis showed that naltrexone and acamprosate are the most effective drugs for AUD, with moderately strong evidence supporting the use of nalmefene and topiramate in some consumption outcomes[120]. Less evidence was found to support the use of disulfiram. These recommendations apply to patients with HCV infection, but the potential for liver toxicity should be considered in patients with liver disease due to alcohol and/or HCV infection. In patients with mild forms of liver disease, anti-craving treatment with naltrexone could be used with caution and monitoring of liver function[121]. However, many of these drugs are potentially harmful to patients with advanced liver disease, due to the risk of liver injury; disulfiram, naltrexone, and nalmefene should be avoided[122,123]. Acamprosate and topiramate may be options in these patients because of mainly renal metabolism and the lack of reported liver toxicity. However, no large clinical trial has supported the continued use of these drugs in patients with advanced liver disease, and no study has focused on patients with ALD and/or HCV infection[124,125]. To date, baclofen is the only drug tested in a randomized control trial including patients with cirrhosis that has shown the benefits of reducing alcohol consumption and craving[126]. A subgroup analysis of data from this trial also reported a positive effect in patients with alcohol dependence and HCV infection[127]. In line with these findings, EASL guidelines recommend baclofen as the only option in patients with advanced ALD[89].

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