World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v22.i4.1411

World J Gastroenterol 2016 January 28; 22(4): 1411-1420
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

2016 Hepatitis C Virus: Global view

Alcoholic liver disease and hepatitis C virus infection

Ignacio Novo-Veleiro, Lucía Alvela-Suárez, Antonio-Javier Chamorro, Rogelio González-Sarmiento, Francisco-Javier Laso, Miguel Marcos

Ignacio Novo-Veleiro, Lucía Alvela-Suárez, Department of Internal Medicine, University Hospital of Santiago de Compostela, 37007 Salamanca, Spain

Ignacio Novo-Veleiro, Antonio-Javier Chamorro, Francisco-Javier Laso, Miguel Marcos, Spanish Working Group on Alcohol and Alcoholism, Spanish Society of Internal Medicine, 28016 Madrid, Spain

Antonio-Javier Chamorro, Francisco-Javier Laso, Miguel Marcos, Alcoholism Unit, Department of Internal Medicine, University Hospital of Salamanca, Institute of Biomedical Research of Salamanca-IBSAL, 37007 Salamanca, Spain

Rogelio González-Sarmiento, Miguel Marcos, Molecular Medicine Unit, Department of Medicine, University of Salamanca, Institute of Biomedical Research of Salamanca-IBSAL, 37007 Salamanca, Spain

Author contributions: Novo-Veleiro I, Alvela-Suárez L and Chamorro AJ carried out the literature research and drafted the manuscript; Novo-Veleiro I, Laso FJ, González-Sarmiento R and Marcos M contributed to manuscript conception and design; all authors approved the final version of the manuscript; Laso FJ and Marcos M contributed equally as senior authors of this manuscript.

Supported by the Spanish Ministry of Science and Innovation, Instituto de Salud Carlos III and the European Union FEDER funds, Una manera de hacer Europa (in part, grant No. PI10/01692 and No. I3SNS-INT12/049 to Marcos M); and the Red de Trastornos Adictivos-RTA (grant No. RD12/0028/0008 to Laso FJ).

Conflict-of-interest statement: Marcos M has received advisory board honoraria from Lundbeck.

Correspondence to: Miguel Marcos, MD, PhD, Assistant Professor, Alcoholism Unit, Department of Internal Medicine, University Hospital of Salamanca, Institute of Biomedical Research of Salamanca-IBSAL, Pº San Vicente, 58-156, 37007 Salamanca, Spain. mmarcos@usal.es
Telephone: +34-923-291100-437
Fax: +34-923-294739

Received: April 28, 2015
Peer-review started: May 6, 2015
First decision: August 31, 2015
Revised: October 1, 2015
Accepted: November 30, 2015
Article in press: December 1, 2015
Published online: January 28, 2016

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

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.

Novo-Veleiro I, Alvela-Suárez L, Chamorro AJ, González-Sarmiento R, Laso FJ, Marcos M. Alcoholic liver disease and hepatitis C virus infection. *World J Gastroenterol* 2016; 22(4): 1411-1420 Available from: URL: http://www.wjgnet.com/1007-9327/full/v22/i4/1411.htm DOI: http://dx.doi.org/10.3748/wjg.v22.i4.1411

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 (approximately 80-120 g/d) 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 $\leqslant$ 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 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].

REFERENCES

1 **Caldwell SH**, Jeffers LJ, Ditomaso A, Millar A, Clark RM, Rabassa A, Reddy KR, De Medina M, Schiff ER. Antibody to hepatitis C is common among patients with alcoholic liver disease with and without risk factors. *Am J Gastroenterol* 1991; **86**: 1219-1223 [PMID: 1652885]

2 **Esteban JI**, Esteban R, Viladomiu L, López-Talavera JC, González A, Hernández JM, Roget M, Vargas V, Genescà J, Buti M. Hepatitis C virus antibodies among risk groups in Spain. *Lancet* 1989; **2**: 294-297 [PMID: 2569102]

3 **Ostapowicz G**, Watson KJ, Locarnini SA, Desmond PV. Role of alcohol in the progression of liver disease caused by hepatitis C virus infection. *Hepatology* 1998; **27**: 1730-1735 [PMID: 9620350 DOI: 10.1002/hep.510270637]

4 **Bode JC**, Biermann J, Kohse KP, Walker S, Bode C. High incidence of antibodies to hepatitis C virus in alcoholic cirrhosis: fact or fiction? *Alcohol Alcohol* 1991; **26**: 111-114 [PMID: 1652249]

5 **Nalpas B**, Thiers V, Pol S, Driss F, Thepot V, Berthelot P, Brechot C. Hepatitis C viremia and anti-HCV antibodies in alcoholics. *J Hepatol* 1992; **14**: 381-384 [PMID: 1380027]

6 **Befrits R**, Hedman M, Blomquist L, Allander T, Grillner L, Kinnman N, Rubio C, Hultcrantz R. Chronic hepatitis C in alcoholic patients: prevalence, genotypes, and correlation to liver disease. *Scand J Gastroenterol* 1995; **30**: 1113-1118 [PMID: 8578173]

7 **Galperim B**, Cheinquer H, Stein A, Fonseca A, Lunge V, Ikuta N. Prevalence of hepatitis C virus in alcoholic patients: role of parenteral risk factors. *Arq Gastroenterol* 2006; **43**: 81-84 [PMID: 17119659]

8 **Novo-Veleiro I**, Calle Cde L, Domínguez-Quibén S, Pastor I, Marcos M, Laso FJ. Prevalence of hepatitis C virus infection in alcoholic patients: cohort study and systematic review. *Alcohol Alcohol* 2013; **48**: 564-569 [PMID: 23690232 DOI: 10.1093/alcalc/agt044]

9 **Bruguera M**, Forns X. [Hepatitis C in Spain]. *Med Clin* (Barc) 2006; **127**: 113-117 [PMID: 16828003]

10 **Armstrong GL**, Wasley A, Simard EP, McQuillan GM, Kuhnert WL, Alter MJ. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. *Ann Intern Med* 2006; **144**: 705-714 [PMID: 16702586 DOI: 10.7326/0003-4819-144-10-200605160-00004]

11 **Wandeler G**, Dufour JF, Bruggmann P, Rauch A. Hepatitis C: a changing epidemic. *Swiss Med Wkly* 2015; **145**: w14093 [PMID: 25658972 DOI: 10.4414/smw.2015.14093]

12 **Hutchinson SJ**, Bird SM, Goldberg DJ. Influence of alcohol on the progression of hepatitis C virus infection: a meta-analysis. *Clin Gastroenterol Hepatol* 2005; **3**: 1150-1159 [PMID: 16271348]

13 **Donato F**, Tagger A, Chiesa R, Ribero ML, Tomasoni V, Fasola M, Gelatti U, Portera G, Boffetta P, Nardi G. Hepatitis B and C virus infection, alcohol drinking, and hepatocellular carcinoma: a case-control study in Italy. Brescia HCC Study. *Hepatology* 1997; **26**: 579-584 [PMID: 9303486 DOI: 10.1002/hep.510260308]

14 **Singal AK**, Guturu P, Hmoud B, Kuo YF, Salameh H, Wiesner RH. Evolving frequency and outcomes of liver transplantation based on etiology of liver disease. *Transplantation* 2013; **95**: 755-760 [PMID: 23370710 DOI: 10.1097/TP.0b013e31827afb3a]

15 **Chen CM**, Yoon YH, Yi HY, Lucas DL. Alcohol and hepatitis C mortality among males and females in the United States: a life table analysis. *Alcohol Clin Exp Res* 2007; **31**: 285-292 [PMID: 17250621 DOI: 10.1111/j.1530-0277.2006.00304.x]

16 **Henry JA**, Moloney C, Rivas C, Goldin RD. Increase in alcohol related deaths: is hepatitis C a factor? *J Clin Pathol* 2002; **55**: 704-707 [PMID: 12195003]

17 **Tsui JI**, Pletcher MJ, Vittinghoff E, Seal K, Gonzales R. Hepatitis C and hospital outcomes in patients admitted with alcohol-related problems. *J Hepatol* 2006; **44**: 262-266 [PMID: 16226823 DOI: 10.1016/j.jhep.2005.07.027]

18 **Hassan MM**, Hwang LY, Hatten CJ, Swaim M, Li D, Abbruzzese JL, Beasley P, Patt YZ. Risk factors for hepatocellular carcinoma: synergism of alcohol with viral hepatitis and diabetes mellitus. *Hepatology* 2002; **36**: 1206-1213 [PMID: 12395331 DOI: 10.1053/jhep.2002.36780]

19 **Wiley TE**, McCarthy M, Breidi L, McCarthy M, Layden TJ. Impact of alcohol on the histological and clinical progression of hepatitis C infection. *Hepatology* 1998; **28**: 805-809 [PMID: 9731576 DOI: 10.1002/hep.510280330]

20 **Bedogni G**, Miglioli L, Masutti F, Ferri S, Castiglione A, Lenzi M, Crocè LS, Granito A, Tiribelli C, Bellentani S. Natural course of chronic HCV and HBV infection and role of alcohol in the general population: the Dionysos Study. *Am J Gastroenterol* 2008; **103**: 2248-2253 [PMID: 18637095 DOI: 10.1111/j.1572-0241.2008.01948.x]

21 **Corrao G**, Aricò S. Independent and combined action of hepatitis C virus infection and alcohol consumption on the risk of symptomatic liver cirrhosis. *Hepatology* 1998; **27**: 914-919 [PMID: 9537428 DOI: 10.1002/hep.510270404]

22 **Khan MH**, Thomas L, Byth K, Kench J, Weltman M, George J, Liddle C, Farrell GC. How much does alcohol contribute to the variability of hepatic fibrosis in chronic hepatitis C? *J Gastroenterol Hepatol* 1998; **13**: 419-426 [PMID: 9641308]

23 **Laso FJ**, Vaquero JM, Almeida J, Marcos M, Orfao A. Chronic alcohol consumption is associated with changes in the distribution, immunophenotype, and the inflammatory cytokine secretion profile of circulating dendritic cells. *Alcohol Clin Exp Res* 2007; **31**: 846-854 [PMID: 17386065 DOI: 10.1111/j.1530-0277.2007.00377.x]

24 **Aloman C**, Gehring S, Wintermeyer P, Kuzushita N, Wands JR. Chronic ethanol consumption impairs cellular immune responses against HCV NS5 protein due to dendritic cell dysfunction. *Gastroenterology* 2007; **132**: 698-708 [PMID: 17258730 DOI: 10.1053/j.gastro.2006.11.016]

25 **Szabo G**, Aloman C, Polyak SJ, Weinman SA, Wands J, Zakhari S. Hepatitis C infection and alcohol use: A dangerous mix for the liver and antiviral immunity. *Alcohol Clin Exp Res* 2006; **30**: 709-719 [PMID: 16573590 DOI: 10.1111/j.1530-0277.2006.00083.x]

26 **Trujillo-Murillo K**, Alvarez-Martínez O, Garza-Rodríguez L, Martínez-Rodríguez H, Bosques-Padilla F, Ramos-Jiménez J, Barrera-Saldaña H, Rincón-Sánchez AR, Rivas-Estilla AM. Additive effect of ethanol and HCV subgenomic replicon expression on COX-2 protein levels and activity. *J Viral Hepat* 2007; **14**: 608-617 [PMID: 17697012 DOI: 10.1111/j.1365-2893.2006.00837.x]

27 **Wang T**, Weinman SA. Causes and consequences of mitochondrial reactive oxygen species generation in hepatitis C. *J Gastroenterol Hepatol* 2006; **21** Suppl 3: S34-S37 [PMID: 16958669 DOI: 10.1111/j.1440-1746.2006.04591.x]

28 **Duguay L**, Coutu D, Hetu C, Joly JG. Inhibition of liver regeneration by chronic alcohol administration. *Gut* 1982; **23**: 8-13 [PMID: 7056500]

29 **Otani K**, Korenaga M, Beard MR, Li K, Qian T, Showalter LA, Singh AK, Wang T, Weinman SA. Hepatitis C virus core protein, cytochrome P450 2E1, and alcohol produce combined mitochondrial injury and cytotoxicity in hepatoma cells. *Gastroenterology* 2005; **128**: 96-107 [PMID: 15633127]

30 **Perlemuter G**, Lettéron P, Carnot F, Zavala F, Pessayre D, Nalpas B, Bréchot C. Alcohol and hepatitis C virus core protein additively increase lipid peroxidation and synergistically trigger hepatic cytokine expression in a transgenic mouse model. *J Hepatol* 2003; **39**: 1020-1027 [PMID: 14642621]

31 **Tikhanovich I**, Kuravi S, Campbell RV, Kharbanda KK, Artigues A, Villar MT, Weinman SA. Regulation of FOXO3 by phosphorylation and methylation in hepatitis C virus infection and alcohol exposure. *Hepatology* 2014; **59**: 58-70 [PMID: 23857333 DOI: 10.1002/hep.26618]

32 **Zhang T**, Li Y, Lai JP, Douglas SD, Metzger DS, O'Brien CP, Ho WZ. Alcohol potentiates hepatitis C virus replicon expression. *Hepatology* 2003; **38**: 57-65 [PMID: 12829987 DOI: 10.1053/jhep.2003.50295]

33 **McCartney EM**, Beard MR. Impact of alcohol on hepatitis C virus replication and interferon signaling. *World J Gastroenterol* 2010; **16**: 1337-1343 [PMID: 20238400 DOI: 10.3748/wjg.v16.i11.1337]

34 **Anand BS**, Thornby J. Alcohol has no effect on hepatitis C virus replication: a meta-analysis. *Gut* 2005; **54**: 1468-1472 [PMID: 16162952 DOI: 10.1136/gut.2004.056697]

35 **Bukong TN**, Hou W, Kodys K, Szabo G. Ethanol facilitates hepatitis C virus replication via up-regulation of GW182 and heat shock protein 90 in human hepatoma cells. *Hepatology* 2013; **57**: 70-80 [PMID: 22898980 DOI: 10.1002/hep.26010]

36 **Hou W**, Bukong TN, Kodys K, Szabo G. Alcohol facilitates HCV RNA replication via up-regulation of miR-122 expression and inhibition of cyclin G1 in human hepatoma cells. *Alcohol Clin Exp Res* 2013; **37**: 599-608 [PMID: 23126531 DOI: 10.1111/acer.12005]

37 **Novo-Veleiro I**, González-Sarmiento R, Cieza-Borrella C, Pastor I, Laso FJ, Marcos M. A genetic variant in the microRNA-146a gene is associated with susceptibility to alcohol use disorders. *Eur Psychiatry* 2014; **29**: 288-292 [PMID: 24630744 DOI: 10.1016/j.eurpsy.2014.02.002]

38 **Bala S**, Marcos M, Kodys K, Csak T, Catalano D, Mandrekar P, Szabo G. Up-regulation of microRNA-155 in macrophages contributes to increased tumor necrosis factor {alpha} (TNF{alpha}) production via increased mRNA half-life in alcoholic liver disease. *J Biol Chem* 2011; **286**: 1436-1444 [PMID: 21062749 DOI: 10.1074/jbc.M110.145870]

39 **Lewohl JM**, Nunez YO, Dodd PR, Tiwari GR, Harris RA, Mayfield RD. Up-regulation of microRNAs in brain of human alcoholics. *Alcohol Clin Exp Res* 2011; **35**: 1928-1937 [PMID: 21651580 DOI: 10.1111/j.1530-0277.2011.01544.x]

40 **Takahashi K**, Takahashi T, Takahashi S, Watanabe K, Boku S, Matsui S, Arai F, Asakura H. Difference in quasispecies of the hypervariable region 1 of hepatitis C virus between alcoholic and non-alcoholic patients. *J Gastroenterol Hepatol* 2001; **16**: 416-423 [PMID: 11354280]

41 **Sherman KE**, Rouster SD, Mendenhall C, Thee D. Hepatitis cRNA quasispecies complexity in patients with alcoholic liver disease. *Hepatology* 1999; **30**: 265-270 [PMID: 10385665 DOI: 10.1002/hep.510300131]

42 **McCullough AJ**, O'Connor JF. Alcoholic liver disease: proposed recommendations for the American College of Gastroenterology. *Am J Gastroenterol* 1998; **93**: 2022-2036 [PMID: 9820369 DOI: 10.1111/j.1572-0241.1998.00587.x]

43 **Zekry A**, McHutchison JG, Diehl AM. Insulin resistance and steatosis in hepatitis C virus infection. *Gut* 2005; **54**: 903-906 [PMID: 15951532 DOI: 10.1136/gut.2004.059873]

44 **Blachier M**, Leleu H, Peck-Radosavljevic M, Valla DC, Roudot-Thoraval F. The burden of liver disease in Europe: a review of available epidemiological data. *J Hepatol* 2013; **58**: 593-608

[PMID: 23419824 DOI: 10.1016/j.jhep.2012.12.005]
45 **Clouston AD**, Jonsson JR, Powell EE. Steatosis as a cofactor in other liver diseases: hepatitis C virus, alcohol, hemochromatosis, and others. *Clin Liver Dis* 2007; **11**: 173-189, x [PMID: 17544978 DOI: 10.1016/j.cld.2007.02.007]
46 **Kohgo Y**, Ohtake T, Ikuta K, Suzuki Y, Hosoki Y, Saito H, Kato J. Iron accumulation in alcoholic liver diseases. *Alcohol Clin Exp Res* 2005; **29**: 189S-193S [PMID: 16344607]
47 **Sebastiani G**, Vario A, Ferrari A, Pistis R, Noventa F, Alberti A. Hepatic iron, liver steatosis and viral genotypes in patients with chronic hepatitis C. *J Viral Hepat* 2006; **13**: 199-205 [PMID: 16475996 DOI: 10.1111/j.1365-2893.2005.00662.x]
48 **Purohit V**, Russo D, Salin M. Role of iron in alcoholic liver disease: introduction and summary of the symposium. *Alcohol* 2003; **30**: 93-97 [PMID: 12957291]
49 **Stickel F**, Hampe J. Genetic determinants of alcoholic liver disease. *Gut* 2012; **61**: 150-159 [PMID: 22110053 DOI: 10.1136/gutjnl-2011-301239]
50 **Schaefer EA**, Chung RT. The impact of human gene polymorphisms on HCV infection and disease outcome. *Semin Liver Dis* 2011; **31**: 375-386 [PMID: 22189977 DOI: 10.1055/s-0031-1297926]
51 **Parsons M**, Campa A, Lai S, Li Y, Martinez JD, Murillo J, Greer P, Martinez SS, Baum MK. Effect of GSTM1-Polymorphism on Disease Progression and Oxidative Stress in HIV Infection: Modulation by HIV/HCV Co-Infection and Alcohol Consumption. *J AIDS Clin Res* 2013; **4**: [PMID: 24416632 DOI: 10.4172/2155-6113.1000237]
52 **Jeng JE**, Tsai HR, Chuang LY, Tsai JF, Lin ZY, Hsieh MY, Chen SC, Chuang WL, Wang LY, Yu ML, Dai CY, Chang JG. Independent and additive interactive effects among tumor necrosis factor-alpha polymorphisms, substance use habits, and chronic hepatitis B and hepatitis C virus infection on risk for hepatocellular carcinoma. *Medicine* (Baltimore) 2009; **88**: 349-357 [PMID: 19910749 DOI: 10.1097/MD.0b013e3181c10477]
53 **Chamorro AJ**, Torres JL, Mirón-Canelo JA, González-Sarmiento R, Laso FJ, Marcos M. Systematic review with meta-analysis: the I148M variant of patatin-like phospholipase domain-containing 3 gene (PNPLA3) is significantly associated with alcoholic liver cirrhosis. *Aliment Pharmacol Ther* 2014; **40**: 571-581 [PMID: 25060292 DOI: 10.1111/apt.12890]
54 **Singal AG**, Manjunath H, Yopp AC, Beg MS, Marrero JA, Gopal P, Waljee AK. The effect of PNPLA3 on fibrosis progression and development of hepatocellular carcinoma: a meta-analysis. *Am J Gastroenterol* 2014; **109**: 325-334 [PMID: 24445574 DOI: 10.1038/ajg.2013.476]
55 **Trépo E**, Nahon P, Bontempi G, Valenti L, Falleti E, Nischalke HD, Hamza S, Corradini SG, Burza MA, Guyot E, Donati B, Spengler U, Hillon P, Toniutto P, Henrion J, Franchimont D, Devière J, Mathurin P, Moreno C, Romeo S, Deltenre P. Association between the PNPLA3 (rs738409 C& gt; G) variant and hepatocellular carcinoma: Evidence from a meta-analysis of individual participant data. *Hepatology* 2014; **59**: 2170-2177 [PMID: 24114809 DOI: 10.1002/hep.26767]
56 **Müller T**, Buch S, Berg T, Hampe J, Stickel F. Distinct, alcohol-modulated effects of PNPLA3 genotype on progression of chronic hepatitis C. *J Hepatol* 2011; **55**: 732-733 [PMID: 21316406 DOI: 10.1016/j.jhep.2011.01.025]
57 **Sookoian S**, Pirola CJ. Meta-analysis of the influence of I148M variant of patatin-like phospholipase domain containing 3 gene (PNPLA3) on the susceptibility and histological severity of nonalcoholic fatty liver disease. *Hepatology* 2011; **53**: 1883-1894 [PMID: 21381068 DOI: 10.1002/hep.24283]
58 **Dongiovanni P**, Donati B, Fares R, Lombardi R, Mancina RM, Romeo S, Valenti L. PNPLA3 I148M polymorphism and progressive liver disease. *World J Gastroenterol* 2013; **19**: 6969-6978 [PMID: 24222941 DOI: 10.3748/wjg.v19.i41.6969]
59 **He S**, McPhaul C, Li JZ, Garuti R, Kinch L, Grishin NV, Cohen JC, Hobbs HH. A sequence variation (I148M) in PNPLA3 associated with nonalcoholic fatty liver disease disrupts triglyceride hydrolysis. *J Biol Chem* 2010; **285**: 6706-6715 [PMID: 20034933 DOI: 10.1074/jbc.M109.064501]
60 **Huang Y**, He S, Li JZ, Seo YK, Osborne TF, Cohen JC, Hobbs HH. A feed-forward loop amplifies nutritional regulation of PNPLA3. *Proc Natl Acad Sci USA* 2010; **107**: 7892-7897 [PMID: 20385813 DOI: 10.1073/pnas.1003585107]
61 **Sarma MP**, Asim M, Medhi S, Bharathi T, Kar P. Hepatitis C virus related hepatocellular carcinoma: a case control study from India. *J Med Virol* 2012; **84**: 1009-1017 [PMID: 22585716 DOI: 10.1002/jmv.23290]
62 **Kiran M**, Chawla YK, Kaur J. Glutathione-S-transferase and microsomal epoxide hydrolase polymorphism and viral-related hepatocellular carcinoma risk in India. *DNA Cell Biol* 2008; **27**: 687-694 [PMID: 18816171 DOI: 10.1089/dna.2008.0805]
63 **Abd El-Moneim E**, Younis FA, Allam N, Gameel K, Osman M. Gene deletion of glutathione S-transferase M1 and T1 and risk factors of hepatocellular carcinoma in Egyptian patients. *Egypt J Immunol* 2008; **15**: 125-134 [PMID: 20306695]
64 **Marcos M**, Pastor I, Chamorro AJ, Ciria-Abad S, González-Sarmiento R, Laso FJ. Meta-analysis: glutathione-S-transferase allelic variants are associated with alcoholic liver disease. *Aliment Pharmacol Ther* 2011; **34**: 1159-1172 [PMID: 21967547 DOI: 10.1111/j.1365-2036.2011.04862.x]
65 **Guo PF**, Jin J, Sun X. Influence of IL10 gene polymorphisms on the severity of liver fibrosis and susceptibility to liver cirrhosis in HBV/HCV-infected patients. *Infect Genet Evol* 2015; **30**: 89-95 [PMID: 25514046 DOI: 10.1016/j.meegid.2014.12.011]
66 **Marcos M**, Pastor I, González-Sarmiento R, Laso FJ. Interleukin-10 gene polymorphism is associated with alcoholism but not with alcoholic liver disease. *Alcohol Alcohol* 2008; **43**: 523-528 [PMID: 18436572 DOI: 10.1093/alcalc/agn026]
67 **Giannitrapani L**, Soresi M, Balasus D, Licata A, Montalto G. Genetic association of interleukin-6 polymorphism (-174 G/C) with chronic liver diseases and hepatocellular carcinoma. *World J Gastroenterol* 2013; **19**: 2449-2455 [PMID: 23674845 DOI: 10.3748/wjg.v19.i16.2449]
68 **Marcos M**, Pastor I, González-Sarmiento R, Laso FJ. Common polymorphisms in interleukin genes (IL4, IL6, IL8 and IL12) are not associated with alcoholic liver disease or alcoholism in Spanish men. *Cytokine* 2009; **45**: 158-161 [PMID: 19185507 DOI: 10.1016/j.cyto.2008.11.003]
69 **Jeng JE**, Tsai JF, Chuang LY, Ho MS, Lin ZY, Hsieh MY, Chen SC, Chuang WL, Wang LY, Yu ML, Dai CY, Chang JG. Tumor necrosis factor-alpha 308.2 polymorphism is associated with advanced hepatic fibrosis and higher risk for hepatocellular carcinoma. *Neoplasia* 2007; **9**: 987-992 [PMID: 18030367]
70 **Talaat RM**, Esmail AA, Elwakil R, Gurgis AA, Nasr MI. Tumor necrosis factor-alpha -308G/A polymorphism and risk of hepatocellular carcinoma in hepatitis C virus-infected patients. *Chin J Cancer* 2012; **31**: 29-35 [PMID: 22200181 DOI: 10.5732/cjc.011.10258]
71 **Radwan MI**, Pasha HF, Mohamed RH, Hussien HI, El-Khshab MN. Influence of transforming growth factor-β1 and tumor necrosis factor-α genes polymorphisms on the development of cirrhosis and hepatocellular carcinoma in chronic hepatitis C patients. *Cytokine* 2012; **60**: 271-276 [PMID: 22682513 DOI: 10.1016/j.cyto.2012.05.010]
72 **Ho SY**, Wang YJ, Chen HL, Chen CH, Chang CJ, Wang PJ, Chen HH, Guo HR. Increased risk of developing hepatocellular carcinoma associated with carriage of the TNF2 allele of the -308 tumor necrosis factor-alpha promoter gene. *Cancer Causes Control* 2004; **15**: 657-663 [PMID: 15280623]
73 **Marcos M**, Gómez-Munuera M, Pastor I, González-Sarmiento R, Laso FJ. Tumor necrosis factor polymorphisms and alcoholic liver disease: a HuGE review and meta-analysis. *Am J Epidemiol* 2009; **170**: 948-956 [PMID: 19755636 DOI: 10.1093/aje/kwp236]
74 World Health Organization. Hepatitis C. (accessed Jul 9, 2014). Available from: URL: http://www.who.int/csr/disease/hepatitis/whocdscsrlyo2003/en/
75 **De Silva HJ**, Vitarana T, Ratnatunga N, Breschkin A, Withane

N, Kularatne WN. Prevalence of hepatitis C virus markers in Sri Lankan patients with alcoholic cirrhosis. *J Gastroenterol Hepatol* 1994; **9**: 381-384 [PMID: 7524722]
76 **Rosman AS**, Paronetto F, Galvin K, Williams RJ, Lieber CS. Hepatitis C virus antibody in alcoholic patients. Association with the presence of portal and/or lobular hepatitis. *Arch Intern Med* 1993; **153**: 965-969 [PMID: 7683191]
77 **Parés A**, Barrera JM, Caballería J, Ercilla G, Bruguera M, Caballería L, Castillo R, Rodés J. Hepatitis C virus antibodies in chronic alcoholic patients: association with severity of liver injury. *Hepatology* 1990; **12**: 1295-1299 [PMID: 2175291]
78 **Nagata S**, Ishii H, Yokoyama H, Kato S, Moriya S, Maruyama K, Takahashi H, Tsuchiya M. Influence of HCV infection and its subtypes on clinical course of alcoholic liver disease. *Gastroenterol Jpn* 1993; **28** Suppl 5: 91-94 [PMID: 7689516]
79 **Coelho-Little ME**, Jeffers LJ, Bernstein DE, Goodman JJ, Reddy KR, de Medina M, Li X, Hill M, La Rue S, Schiff ER. Hepatitis C virus in alcoholic patients with and without clinically apparent liver disease. *Alcohol Clin Exp Res* 1995; **19**: 1173-1176 [PMID: 8561287]
80 **Schmidt CS**, Schön D, Schulte B, Lüth S, Polywka S, Reimer J. Viral hepatitis in alcohol-dependent inpatients: prevalence, risk factors, and treatment uptake. *J Addict Med* 2013; **7**: 417-421 [PMID: 24189174 DOI: 10.1097/ADM.0b013e3182a50817]
81 **Kabiri M**, Jazwinski AB, Roberts MS, Schaefer AJ, Chhatwal J. The changing burden of hepatitis C virus infection in the United States: model-based predictions. *Ann Intern Med* 2014; **161**: 170-180 [PMID: 25089861 DOI: 10.7326/M14-0095]
82 **Brillanti S**, Masci C, Siringo S, Di Febo G, Miglioli M, Barbara L. Serological and histological aspects of hepatitis C virus infection in alcoholic patients. *J Hepatol* 1991; **13**: 347-350 [PMID: 1667017]
83 **Saigal S**, Kapoor D, Tandon N, Thakur V, Guptan RC, Agarwal SR, Sarin SK. High seroprevalence and clinical significance of hepatitis B and C infection in hospitalized patients with alcoholic cirrhosis. *J Assoc Physicians India* 2002; **50**: 1002-1006 [PMID: 12421019]
84 **Sata M**, Fukuizumi K, Uchimura Y, Nakano H, Ishii K, Kumashiro R, Mizokami M, Lau JY, Tanikawa K. Hepatitis C virus infection in patients with clinically diagnosed alcoholic liver diseases. *J Viral Hepat* 1996; **3**: 143-148 [PMID: 8871873]
85 **Kwon SY**, Ahn MS, Chang HJ. Clinical significance of hepatitis C virus infection to alcoholics with cirrhosis in Korea. *J Gastroenterol Hepatol* 2000; **15**: 1282-1286 [PMID: 11129222]
86 **Verbaan H**, Andersson K, Eriksson S. Intravenous drug abuse--the major route of hepatitis C virus transmission among alcohol-dependent individuals? *Scand J Gastroenterol* 1993; **28**: 714-718 [PMID: 7692588]
87 **González Quintela A**, Alende R, Aguilera A, Tomé S, Gude F, Pérez Becerra E, Torre A, Martínez Vázquez JM, Barrio E. [Hepatitis C virus antibodies in alcoholic patients]. *Rev Clin Esp* 1995; **195**: 367-372 [PMID: 7644783]
88 **Jiang JJ**, Dubois F, Driss F, Carnot F, Thepot V, Pol S, Berthelot P, Brechot C, Nalpas B. Clinical impact of drug addiction in alcoholics. *Alcohol Alcohol* 1995; **30**: 55-60 [PMID: 7538299]
89 **European Association for the Study of Liver**. EASL clinical practical guidelines: management of alcoholic liver disease. *J Hepatol* 2012; **57**: 399-420 [PMID: 22633836 DOI: 10.1016/j.jhep.2012.04.004]
90 **Smith BD**, Morgan RL, Beckett GA, Falck-Ytter Y, Holtzman D, Teo CG, Jewett A, Baack B, Rein DB, Patel N, Alter M, Yartel A, Ward JW. Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945-1965. *MMWR Recomm Rep* 2012; **61**: 1-32 [PMID: 22895429]
91 **European Association for the Study of the Liver**. EASL recommendations on treatment of hepatitis C 2014. *J Hepatol* 2014; **61**: 373-395 [PMID: 24818984 DOI: 10.1016/j.jhep.2014.05.001]
92 **Naveau S**, Gaudé G, Asnacios A, Agostini H, Abella A, Barri-Ova N, Dauvois B, Prévot S, Ngo Y, Munteanu M, Balian A, Njiké-Nakseu M, Perlemuter G, Poynard T. Diagnostic and prognostic values of noninvasive biomarkers of fibrosis in patients with alcoholic liver disease. *Hepatology* 2009; **49**: 97-105 [PMID: 19053048 DOI: 10.1002/hep.22576]
93 **Mueller S**, Millonig G, Sarovska L, Friedrich S, Reimann FM, Pritsch M, Eisele S, Stickel F, Longerich T, Schirmacher P, Seitz HK. Increased liver stiffness in alcoholic liver disease: differentiating fibrosis from steatohepatitis. *World J Gastroenterol* 2010; **16**: 966-972 [PMID: 20180235 DOI: 10.3748/wjg.v16.i8.966]
94 **Sulkowski MS**, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson I, Lawitz E, Lok AS, Hinestrosa F, Thuluvath PJ, Schwartz H, Nelson DR, Everson GT, Eley T, Wind-Rotolo M, Huang SP, Gao M, Hernandez D, McPhee F, Sherman D, Hindes R, Symonds W, Pasquinelli C, Grasela DM. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. *N Engl J Med* 2014; **370**: 211-221 [PMID: 24428467 DOI: 10.1056/NEJMoa1306218]
95 **Rodriguez-Torres M**, Lawitz E, Kowdley KV, Nelson DR, Dejesus E, McHutchison JG, Cornpropst MT, Mader M, Albanis E, Jiang D, Hebner CM, Symonds WT, Berrey MM, Lalezari J. Sofosbuvir (GS-7977) plus peginterferon/ribavirin in treatment-naïve patients with HCV genotype 1: a randomized, 28-day, dose-ranging trial. *J Hepatol* 2013; **58**: 663-668 [PMID: 23183528 DOI: 10.1016/j.jhep.2012.11.018]
96 **Forns X**, Lawitz E, Zeuzem S, Gane E, Bronowicki JP, Andreone P, Horban A, Brown A, Peeters M, Lenz O, Ouwerkerk-Mahadevan S, Scott J, De La Rosa G, Kalmeijer R, Sinha R, Beumont-Mauviel M. Simeprevir with peginterferon and ribavirin leads to high rates of SVR in patients with HCV genotype 1 who relapsed after previous therapy: a phase 3 trial. *Gastroenterology* 2014; **146**: 1669-1679.e3 [PMID: 24602923 DOI: 10.1053/j.gastro.2014.02.051]
97 **Jacobson IM**, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, Shiffman ML, Lawitz E, Everson G, Bennett M, Schiff E, Al-Assi MT, Subramanian GM, An D, Lin M, McNally J, Brainard D, Symonds WT, McHutchison JG, Patel K, Feld J, Pianko S, Nelson DR. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med* 2013; **368**: 1867-1877 [PMID: 23607593 DOI: 10.1056/NEJMoa1214854]
98 **Lawitz E**, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, Schultz M, Davis MN, Kayali Z, Reddy KR, Jacobson IM, Kowdley KV, Nyberg L, Subramanian GM, Hyland RH, Arterburn S, Jiang D, McNally J, Brainard D, Symonds WT, McHutchison JG, Sheikh AM, Younossi Z, Gane EJ. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med* 2013; **368**: 1878-1887 [PMID: 23607594 DOI: 10.1056/NEJMoa1214853]
99 **Zeuzem S**, Dusheiko GM, Salupere R, Mangia A, Flisiak R, Hyland RH, Illeperuma A, Svarovskaia E, Brainard DM, Symonds WT, Subramanian GM, McHutchison JG, Weiland O, Reesink HW, Ferenci P, Hézode C, Esteban R. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. *N Engl J Med* 2014; **370**: 1993-2001 [PMID: 24795201 DOI: 10.1056/NEJMoa1316145]
100 **American Association for the Study of Liver Diseases**. Recommendations for testing, Managing, and Treating Hepatitis C. (accessed Dec 4, 2015). Available from: URL: http://www.hcvguidelines.org/
101 **Afdhal N**, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, Romero-Gomez M, Zarski JP, Agarwal K, Buggisch P, Foster GR, Bräu N, Buti M, Jacobson IM, Subramanian GM, Ding X, Mo H, Yang JC, Pang PS, Symonds WT, McHutchison JG, Muir AJ, Mangia A, Marcellin P. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med* 2014; **370**: 1889-1898 [PMID: 24725239 DOI: 10.1056/NEJMoa1402454]
102 **Afdhal N**, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, Nahass R, Ghalib R, Gitlin N, Herring R, Lalezari J, Younes ZH, Pockros PJ, Di Bisceglie AM, Arora S, Subramanian GM, Zhu Y, Dvory-Sobol H, Yang JC, Pang PS, Symonds WT, McHutchison JG, Muir AJ, Sulkowski M, Kwo P. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *N Engl J Med* 2014; **370**: 1483-1493 [PMID: 24725238 DOI: 10.1056/NEJMoa1316366]
103 **Chayama K**, Notsumata K, Kurosaki M, Sato K, Rodrigues

L, Setze C, Badri P, Pilot-Matias T, Vilchez RA, Kumada H. Randomized trial of interferon- and ribavirin-free ombitasvir/paritaprevir/ritonavir in treatment-experienced hepatitis C virus-infected patients. *Hepatology* 2015; **61**: 1523-1532 [PMID: 25644279 DOI: 10.1002/hep.27705]

104 **Le Lan C**, Guillygomarc'h A, Danielou H, Le Dréau G, Lainé F, Védeilhié C, Deugnier Y, Brissot P, Guyader D, Moirand R. A multi-disciplinary approach to treating hepatitis C with interferon and ribavirin in alcohol-dependent patients with ongoing abuse. *J Hepatol* 2012; **56**: 334-340 [PMID: 21756854 DOI: 10.1016/j.jhep.2011.05.021]

105 **Bruggmann P**, Dampz M, Gerlach T, Kravecz L, Falcato L. Treatment outcome in relation to alcohol consumption during hepatitis C therapy: an analysis of the Swiss Hepatitis C Cohort Study. *Drug Alcohol Depend* 2010; **110**: 167-171 [PMID: 20334985 DOI: 10.1016/j.drugalcdep.2010.02.016]

106 **Okazaki T**, Yoshihara H, Suzuki K, Yamada Y, Tsujimura T, Kawano K, Yamada Y, Abe H. Efficacy of interferon therapy in patients with chronic hepatitis C. Comparison between non-drinkers and drinkers. *Scand J Gastroenterol* 1994; **29**: 1039-1043 [PMID: 7871371]

107 **Anand BS**, Currie S, Dieperink E, Bini EJ, Shen H, Ho SB, Wright T. Alcohol use and treatment of hepatitis C virus: results of a national multicenter study. *Gastroenterology* 2006; **130**: 1607-1616 [PMID: 16697724 DOI: 10.1053/j.gastro.2006.02.023]

108 **Bacon BR**, Gordon SC, Lawitz E, Marcellin P, Vierling JM, Zeuzem S, Poordad F, Goodman ZD, Sings HL, Boparai N, Burroughs M, Brass CA, Albrecht JK, Esteban R. Boceprevir for previously treated chronic HCV genotype 1 infection. *N Engl J Med* 2011; **364**: 1207-1217 [PMID: 21449784 DOI: 10.1056/NEJMoa1009482]

109 **Poordad F**, McCone J, Bacon BR, Bruno S, Manns MP, Sulkowski MS, Jacobson IM, Reddy KR, Goodman ZD, Boparai N, DiNubile MJ, Sniukiene V, Brass CA, Albrecht JK, Bronowicki JP. Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med* 2011; **364**: 1195-1206 [PMID: 21449783 DOI: 10.1056/NEJMoa1010494]

110 **Benhamou Y**, Moussalli J, Ratziu V, Lebray P, De Backer K, De Meyer S, Ghys A, Luo D, Picchio GR, Beumont M. Telaprevir activity in treatment-naive patients infected hepatitis C virus genotype 4: a randomized trial. *J Infect Dis* 2013; **208**: 1000-1007 [PMID: 23801602 DOI: 10.1093/infdis/jit274]

111 **Sherman KE**, Flamm SL, Afdhal NH, Nelson DR, Sulkowski MS, Everson GT, Fried MW, Adler M, Reesink HW, Martin M, Sankoh AJ, Adda N, Kauffman RS, George S, Wright CI, Poordad F. Response-guided telaprevir combination treatment for hepatitis C virus infection. *N Engl J Med* 2011; **365**: 1014-1024 [PMID: 21916639 DOI: 10.1056/NEJMoa1014463]

112 **American Psychiatric Association**. Diagnostic and statistical manual of mental disorders. 5th ed. Arlington: American Psychiatric Publishing, 2013

113 **Addolorato G**, Mirijello A, Leggio L, Ferrulli A, Landolfi R. Management of alcohol dependence in patients with liver disease. *CNS Drugs* 2013; **27**: 287-299 [PMID: 23456576 DOI: 10.1007/s40263-013-0043-4]

114 **Bohn MJ**, Babor TF, Kranzler HR. The Alcohol Use Disorders Identification Test (AUDIT): validation of a screening instrument for use in medical settings. *J Stud Alcohol* 1995; **56**: 423-432 [PMID: 7674678]

115 **Lim JK**, Tate JP, Fultz SL, Goulet JL, Conigliaro J, Bryant KJ, Gordon AJ, Gibert C, Rimland D, Goetz MB, Klein MB, Fiellin DA, Justice AC, Lo Re V. Relationship between alcohol use categories and noninvasive markers of advanced hepatic fibrosis in HIV-infected, chronic hepatitis C virus-infected, and uninfected patients. *Clin Infect Dis* 2014; **58**: 1449-1458 [PMID: 24569533 DOI: 10.1093/cid/ciu097]

116 **World Health Organization**. Guidelines for the screening, care and treatment of persons with hepatitis C infection. (accessed Jul 21, 2014). Available from: URL: http://www.who.int/hiv/pub/hepatitis/hepatitis-c-guidelines/en/

117 **World Health Organization**. The ASSIST project - Alcohol, Smoking and Substance Involvement Screening Test. (accessed 2014 Jul 21). Available from: URL: http://www.who.int/substance_abuse/activities/assist/en/

118 **World Health Organization**. The ASSIST-linked brief intervention for hazardous and harmful substance use. (accessed Aug 18, 2014). Available from: URL: http://www.who.int/substance_abuse/publications/en/

119 **National Institute on Alcohol Abuse and Alcoholism**. Helping patients who drink too much. A clinician's guideline. (accessed Aug 18, 2014). Available from: URL: http://pubs.niaaa.nih.gov/publications/Practitioner/CliniciansGuide2005/clinicians_guide.htm

120 **Jonas DE**, Amick HR, Feltner C, Bobashev G, Thomas K, Wines R, Kim MM, Shanahan E, Gass CE, Rowe CJ, Garbutt JC. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. *JAMA* 2014; **311**: 1889-1900 [PMID: 24825644 DOI: 10.1001/jama.2014.3628]

121 **Lucey MR**, Silverman BL, Illeperuma A, O'Brien CP. Hepatic safety of once-monthly injectable extended-release naltrexone administered to actively drinking alcoholics. *Alcohol Clin Exp Res* 2008; **32**: 498-504 [PMID: 18241321 DOI: 10.1111/j.1530-0277.2007.00593.x]

122 **Forns X**, Caballería J, Bruguera M, Salmerón JM, Vilella A, Mas A, Parés A, Rodés J. Disulfiram-induced hepatitis. Report of four cases and review of the literature. *J Hepatol* 1994; **21**: 853-857 [PMID: 7890903]

123 **Atkinson RL**, Berke LK, Drake CR, Bibbs ML, Williams FL, Kaiser DL. Effects of long-term therapy with naltrexone on body weight in obesity. *Clin Pharmacol Ther* 1985; **38**: 419-422 [PMID: 4042525]

124 **Vuittonet CL**, Halse M, Leggio L, Fricchione SB, Brickley M, Haass-Koffler CL, Tavares T, Swift RM, Kenna GA. Pharmacotherapy for alcoholic patients with alcoholic liver disease. *Am J Health Syst Pharm* 2014; **71**: 1265-1276 [PMID: 25027533 DOI: 10.2146/ajhp140028]

125 **Mozayani A**, Carter J, Nix R. Distribution of topiramate in a medical examiner's case. *J Anal Toxicol* 1999; **23**: 556-558 [PMID: 10517568]

126 **Addolorato G**, Leggio L, Ferrulli A, Cardone S, Bedogni G, Caputo F, Gasbarrini G, Landolfi R. Dose-response effect of baclofen in reducing daily alcohol intake in alcohol dependence: secondary analysis of a randomized, double-blind, placebo-controlled trial. *Alcohol Alcohol* 2011; **46**: 312-317 [PMID: 21414953 DOI: 10.1093/alcalc/agr017]

127 **Leggio L**, Ferrulli A, Zambon A, Caputo F, Kenna GA, Swift RM, Addolorato G. Baclofen promotes alcohol abstinence in alcohol dependent cirrhotic patients with hepatitis C virus (HCV) infection. *Addict Behav* 2012; **37**: 561-564 [PMID: 22244707 DOI: 10.1016/j.addbeh.2011.12.010]

P- Reviewer: Robaeys GKMM, Streba LAM, Trabut JB
S- Editor: Yu J **L- Editor**: A **E- Editor**: Liu XM

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 1007-9327
0 4>
9 771007 932045