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TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (2): Hepatitis C virus

Alcoholic hepatitis and concomitant hepatitis C virus infection

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Core tip: The article describes prevalence of hepatitis C virus infection and its impact on outcomes among patients with alcoholic hepatitis. The article deals with controversies and lack of guidelines on treating alcoholic hepatitis patients especially use of corticosteroids in this sick patient population.

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Abstract

Hepatitis C virus (HCV) infection and alcohol abuse are two most important causes of chronic liver disease in the United States. Alcoholic hepatitis is a unique clinical syndrome among patients with chronic and active alcohol abuse with a potential for high short-term mortality. About 20% of patients presenting with alcoholic hepatitis have concomitant HCV infection. Mortality from alcoholic hepatitis is increased in the presence of concomitant hepatitis C due to synergistic interaction between HCV and alcohol in causing hepatocellular damage. Large prospective randomized studies are needed to develop guidelines on the use of corticosteroids among patients with alcoholic hepatitis and concomitant HCV infection. The impact of antiviral therapy on mortality and outcome in the setting of alcoholic hepatitis remains a novel area for future research.

INTRODUCTION

Hepatitis C virus (HCV) infection and alcohol abuse are two leading causes of liver cirrhosis in the United States contributing to about 60% of all cases of chronic liver disease and about half of all liver transplants in the United States[1,2]. It is estimated that about 4.1 million people in the United States have been infected with HCV of whom 3.2 million are still living with the infection[3]. About 60% of people in the United States report use of alcohol at some point in their life time with 8%-10% people reporting heavy alcohol use (> 2 drinks/d in males and > 1 drink/d in females). Lifetime prevalence of alcohol abuse is 17.8% and of alcohol dependence is 12.5%. Liver related mortality from alcohol is 4% of mortality and 5% of disability globally; the highest burden is in Europe where the mortality is 7% and disability is 12%[4]. Spectrum of alcoholic liver disease (ALD) among people with alcohol abuse includes steatosis or fatty liver in over 90%, alcoholic liver injury in 30%-35%, alcoholic

Table 1 Prevalence of hepatitis C virus antibodies and hepatitis C virus-RNA in patients with alcoholic hepatitis

Ref.	Sample size	HCV antibodies	HCVRNA	Liver biopsy
Parés *et al*[10]	14	21.4%	NA	100%
Nishiguchi *et al*[11]	20	40%	15%	100%
Nalpas *et al*[12]	26	35.4%	30%	69.2%
Bode *et al*[13]	15	6.70%	NA	100%
Rosman *et al*[14]	5	20%	NA	100%
Sata *et al*[15]	27	37%	22%	100%
Tanaka *et al*[16]	24	25%	8.3%	100%
Pandya *et al*[17]	4129	24.9%	NA	NA
Singal *et al*[18]	76	38.1%	NA	9%
Novo-Veleiro *et al*[19]	6	0%	NA	100

HCV: Hepatitis C virus; NA: Not available.

cirrhosis in 10%-20%, and hepatocellular carcinoma in 3%-8%[5].

About one third to half of patients with ALD and active alcohol abuse may develop a unique clinical syndrome of alcoholic hepatitis comprising of combination of the following symptoms or signs (1) acute liver failure; (2) deep jaundice; (3) encephalopathy; (4) features of systemic inflammatory response syndrome in the absence of sepsis or cholangitis: fever, leukocytosis, tender hepatomegaly; and (5) hepatic bruit. About 80% of alcoholic hepatitis patients have established cirrhosis and patients with severe episode of alcoholic hepatitis [modified discriminant function (mDF) > 32] have a potential for 40%-50% mortality within a month of presentation[6,7]. Prevalence of HCV and its interaction with alcoholic hepatitis is not well described and the data on this are scanty. In this article we review the prevalence, presentation, and outcomes of alcoholic hepatitis patients who have concomitant HCV infection.

PREVALENCE OF HEPATITIS C IN ALCOHOLIC HEPATITIS PATIENTS

Concomitant HCV infection and alcohol abuse are known to synergistically act in causing more severe liver disease, rapid progression of fibrosis, and higher prevalence of hepatocellular carcinoma (HCC). Combined HCV and alcohol account for about 10%-14% of all cases of cirrhosis and for about 8%-10% of all liver transplants in the United States[1,2]. The prevalence of anti-HCV is higher in alcoholics *vs* nonalcoholic patients (10% *vs* 0%, $P > 0.01$)[8]. Factors such as high risk sexual behavior, intravenous drug user, and higher risk for trauma and accidents requiring blood transfusions and interventions are some of the potential reasons for this higher prevalence of HCV in alcoholics[9].

Pooled homogeneous data without publication bias from 10 studies ($n = 4342$) in patients with alcoholic hepatitis shows the prevalence of HCV antibodies to be 25.4% (95%CI: 24.2-26.7) and of HCVRNA from 4 of these studies ($n = 97$) to be 21.2 (95%CI: 13.9-31)[10-19] (Table 1).

Differences on study population, study design, country of origin, and time period with different ELISA testing used may possibly explain variation across studies on the HCV prevalence (Table 1). In a recent analysis of the National Inpatient Sample (NIS) database, prevalence of HCV in alcoholic hepatitis patients was shown increasing by 150% with a current prevalence of HCV in alcoholic hepatitis in 2007 to be around 7%-8%. The increase in HCV prevalence in alcoholic hepatitis patients was shown to be due to increase in the diagnosis of HCV as there was also an increasing prevalence of HCV in admitted patients in the same calendar year who did not have alcoholic hepatitis[20]. This is likely due to increasing awareness on HCV with physician practices increasing to check for HCV as shown in a recent survey where 93% of 488 gastroenterologists and hepatologists reported testing for HCV in their patients with alcoholic hepatitis[7]. It is unclear whether the associated HCV infection predisposes an individual to develop alcoholic hepatitis. However, factors associated with concomitant HCV positivity in alcoholic hepatitis patients were reported in an analysis of the NIS database as age (40-60 years *vs* < 40 years: 8% *vs* 4.8%), ethnicity (Hispanic and African-American *vs* Caucasians: 7.4% *vs* 6.5% and 7.8% *vs* 6.5%), charlson comorbidity index score, complications of cirrhosis such as variceal hemorrhage and hepatic encephalopathy, and teaching status of the hospital[20].

IMPACT OF HEPATITIS C ON OUTCOME OF ALCOHOLIC HEPATITIS

There are many studies reporting worse and severe alcoholic cirrhosis in HCV positive drinkers. Higher inpatient mortality occurred in patients alcoholics with HCV infection compared to non drinkers (4.4% *vs* 2.4%, $P < 0.01$)[21]. Another study related a marked increase in mortality (243%) in alcoholics to increased prevalence of HCV over the same period[22]. However, data on the impact of HCV on course and severity of alcoholic hepatitis are scanty. In a retrospective study on 76 alcoholic hepatitis patients (27 concomitantly HCV positive), a total of 13 (16%) patients died at 6 mo from alcoholic hepatitis diagnosis. Although, proportion of patients with severe disease was similar at presentation in HCV positive and negative patients (59% *vs* 49%, $P = 0.18$), HCV positive patients were more likely to die to 6 mo (31% *vs* 9%, $P = 0.015$). In a multivariable cox proportional hazard regression model controlling for treatment for alcoholic hepatitis in addition to patient demographics and disease severity at presentation, HCV positive patients were over 8 times likely to die compared to HCV negative patients[18]. Similar data were reported using large VA database of 4129 patients with alcoholic hepatitis out of those 1028 had HCV (24.9%). The mortality at 90-d from alcoholic hepatitis was higher in HCV positive patients compared to HCV negative patients (15.7% *vs* 8.1%, $P = 0.0007$), the impact of HCV infection on mortality was particu-

larly significant in non-cirrhotic[17]. In an analysis of NIS database of over 100000 alcoholic hepatitis patients admitted during 1998 and 2007 in the United States, the in-hospital mortality from alcoholic hepatitis was about 3.2%, higher among HCV positive compared to HCV negative alcoholic hepatitis patients (3.8% *vs* 3.1%, P = 0.001). Limitations of a database analysis using ICD-09 code, lack of information on disease severity with inclusion of mild disease, and lack of outpatient information after the hospital discharge could possibly account for a low mortality from alcoholic hepatitis in this analysis. Although, in-hospital mortality from alcoholic hepatitis reduced annually at 7% between 1998 and 2007, HCV positive alcoholic hepatitis patients remained 30% more likely to die after adjusting for patient and disease characteristics including controlling for calendar year[20].

In a recent analysis of all patients admitted with discharge diagnosis of alcoholic hepatitis during 1988 and 2007 in the United States, the in-hospital mortality was higher among patients with concomitant HCV infection compared to alcoholic hepatitis patients alone (41.1% *vs* 3.2%, P = 0.07). In this study, length of stay and cost of hospitalization were also increased in the group with concomitant HCV and alcoholic hepatitis[23]. It remains to be seen whether addition of HCV into the scoring severity model would further improve the accuracy of currently existing scoring systems to predict disease severity and outcomes.

PATHOGENESIS OF INTERACTION OF HEPATITIS C AND ALCOHOLIC HEPATITIS

Mechanisms of interaction of alcohol and HCV are complex and remain incompletely understood. Both alcohol and HCV can cause the full spectrum of ALD including steatosis, steatohepatitis, cirrhosis, and HCC. Alcohol leads to steatosis by inducing lipogenesis while HCV causes steatosis by interruption of beta oxidation of fatty. Liver disease initiated by both alcohol and HCV leads to inflammation with cytokine signaling, generation of reactive oxygen species (ROS), depletion of antioxidants such as glutathione, increasing iron accumulation in the liver, and liver fibrosis[24]. Various sources for ROS from ethanol injury are CYP2E1 stimulation by ethanol, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase as alcohol increases conversion of NAD to NADPH, alcohol metabolic products such as acetaldehyde, cytokine induced apoptosis and cell death, and hypomethylation of DNA[6,7]. In addition, HCV core protein causes mitochondrial defects increasing generation of ROS[25]. Hence, oxidative stress seems to be hallmark of this synergy with downstream effects of lipid peroxidation and increasing levels of transforming growth factor-β resulting in liver fibrosis[26]. *In vitro*, these effects have been shown to be prevented by the antioxidant *n*-acetylcysteine[25].

At the more cellular level, HCV core protein has been shown to increase calcium entry into the mitochondria which further increase ROS generation[25]. This whole process primes these infected mitochondria to Calcium and ROS mediated oxidative stress and cell death. In alcohol fed mice the injury from alcohol has been shown to be most severe in superoxide dismutase (antioxidant) knockout HCV transgenic mice followed by HCV transgenic mice which are wild type for SOD followed by mice wild type for both SOD and HCV[27]. Recently data are emerging on the mechanisms of HCV impacts cell cycle and antioxidant levels in causing alcohol mediated injury. Animal data have shown that HCV induces changes in FOXO3 (a factor controlling cell proliferation and antioxidant levels) post-translational modification leading to more severe injury[28]. In another study, FOXO3 function impairment and oxidative stress was shown to be increased in the presence of combined HCV and alcohol compared to presence of either agent alone[29]. Angiopoietin-like 3 gene expression is also decreased with exposure to HCV which leads to increased uptake of lipids from the plasma to liver cells, a mechanism thought to help viral replication[30]. Future studies with clearer understanding of pathogenesis of cellular pathways in synergistic action of HCV and alcohol in causing ALD and alcoholic hepatitis would be crucial in developing newer targets and drugs for treating patients with ALD and/or alcoholic hepatitis.

MANAGEMENT OF ALCOHOLIC HEPATITIS IN HEPATITIS C POSITIVE PATIENTS

Corticosteroids remain the first line option for treating severe episode of alcoholic hepatitis (mDF > 32 and/or the presence of hepatic encephalopathy) and provide about 50% survival benefit in severe alcoholic hepatitis with 15%-20% patients still dying within a month in spite of treatment with these drugs[31]. Mechanisms of non-response to steroids which is reported in 40%-50% of severe alcoholic hepatitis patients remain unclear[32]. Pentoxifylline is an option based on center or physician choice or for patients who cannot receive corticosteroids for contraindications to these medications[7,33]. Potential contraindications for use of steroids in severe alcoholic hepatitis include active infection, gastrointestinal bleeding, acute pancreatitis, and very poorly controlled diabetes. Renal failure or hepatorenal syndrome is also considered a contraindication for the use of steroids as these patients do not respond to steroids in the presence of this disease complication[34]. Adjuvant use of *n*-acetylcysteine in combination with steroids was shown to be better than steroids alone for the outcome of mortality at 1 mo among patients with severe alcoholic hepatitis (8% *vs* 24%, P = 0.006). However there was no significant difference in mortality at six month between the two groups (27% *vs* 38%, P = 0.07)[35].

In most randomized controlled studies evaluating ste-

roids, pentoxifylline, and NAC patients with concomitant HCV have been excluded. Concomitant HCV infection is not recommended to be a contraindication for use of steroid treatment in alcoholic hepatitis patients[36]. Hence, given paucity of how to treat alcoholic hepatitis in the presence of concomitant HCV, there remains lack of guidelines on the management of this group of patients. A recent survey evaluated the use of corticosteroids by gastroenterologists and hepatologists for treatment of severe alcoholic hepatitis in the presence of HCV. With a survey response rate of 27%, out of 416 gastroenterologists and hepatologists, only about 47% reported that they would use corticosteroids in the treatment of severe alcoholic hepatitis and 75% reported that they would not change the approach to treatment irrespective of concomitant HCV infection. However, when asked on treatment choice for HCV positive alcoholic hepatitis patients, only 4% chose steroids to treat HCV positive alcoholic hepatitis. These contradictory responses of gastroenterologists and hepatologists form the basis for need for guidelines on use of steroids in HCV positive alcoholic hepatitis patients[37].

The general fear among physicians is increase in HCV replication via the immunosuppressive effect of steroids with possible worsening of the disease. However, the data on the impact of steroids on the HCV replication is scant. In an *in-vitro* study, steroids showed no increase in HCV replication. One intriguing observation in the study was the rebound of the immune response to HCV with the potential for accelerated cell damage with quick tapper of the steroids[38]. A large meta-analysis encompassing a total of 2305 patients concluded that there was no statistically significant difference in the recurrence of HCV infection associated with the use of corticosteroids compared to corticosteroids free regimen when each study is looked at individually. Collectively the meta-analysis showed decreased recurrence of HCV infection with steroids avoidance in those liver transplant recipients (RR = 0.90, $P = 0.03$)[39]. However, heterogeneous population was a limitation of this meta-analysis.

Further, the risk of increasing HCV replication with corticosteroids is associated with their use in bolus high doses or for long time followed by taper. Use of steroids in alcoholic hepatitis patients is limited to a short period of 4 wk in a dose of prednisolone 40 mg/d. Hence, the available literature is insufficient to recommend against the use of corticosteroids for treating alcoholic hepatitis patients in the presence of concomitant HCV infection suggesting need for more data and randomized studies to address this issue as a basis of guidelines on treating this population of patients.

It remains to be seen if the treatment of hepatitis C infection in those who present with alcoholic hepatitis using antiviral therapy along with the standard management would impact the survival of those patients. Given the current interferon (IFN) based regimens, such an approach seems non-viable and ethical in these very sick patients. Treatment of HCV in alcoholic hepatitis patients with the emerging IFN free regimens with shorter duration and better safety profile may be a promising approach and remains a testable hypothesis within the controlled limits of a clinical trial as the field of HCV treatment rapidly evolves[40].

Patients who remain unresponsive to treatment with steroids or pentoxifylline have a high mortality at a short interval and current options to manage these patients are limited. Given requirement of minimum of 6 mo of abstinence prior to initiating liver transplant evaluation, this treatment modality cannot be applied to these patients. Emerging encouraging data on the beneficial outcome of select patients with alcoholic hepatitis with liver transplantation brings ray of hope for these patients[41,42]. However, given the shortage of donor organs, we need more prospective data from other centers and on larger number of patients before implementing liver transplantation for alcoholic hepatitis patients.

CONCLUSION

Concomitant HCV infection is frequently present in patients with alcoholic hepatitis and impacts its outcome negatively. Treatment of HCV positive alcoholic hepatitis patients remains a clinical challenge with need for further research aiming at formulation of guidelines on management of these patients.

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