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REVIEW

Hepatocellular carcinoma in non-alcoholic steatohepatitis: Current knowledge and implications for management

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Abstract

With the prevalence of hepatitis C virus expected to decline, the proportion of hepatocellular carcinoma (HCC) related to non-alcoholic steatohepatitis (NASH) is anticipated to increase exponentially due to the growing epidemic of obesity and diabetes. The annual incidence rate of developing HCC in patients with NASH-related cirrhosis is not clearly understood with rates ranging from 2.6%-12.8%. While multiple new mechanisms have been implicated in the development of HCC in NASH; further prospective long-term studies are needed to validate these findings. Recent evidence has shown a significant proportion of patients with non-alcoholic fatty liver disease and NASH progress to HCC in the absence of cirrhosis. Liver resection and transplantation represent curative therapeutic options in select NASH-related HCC patients but have placed a significant burden to our healthcare resources and utilization. Currently NASH-related HCC is the fastest growing indication for liver transplant in HCC candidates. Increased efforts to implement effective screening and preventative strategies, particularly in non-cirrhotic NASH patients, are needed to reduce the future impact imposed by NASH-related HCC.

Key words: Non-alcoholic steatohepatitis; Cirrhosis; Non-alcoholic fatty liver disease; Obesity; Hepatocellular carcinoma

Core tip: Non-alcoholic steatohepatitis (NASH) is antici-

pated to account for a greater proportion of hepatocellular carcinoma (HCC) incidence due to the growing epidemic of obesity and diabetes. Currently NASH-related HCC is the fastest growing indication for liver transplant in HCC candidates. Increased efforts to implement effective screening and preventative strategies particularly in non-cirrhotic NASH patients possibly based on genetic susceptibility are needed to reduce the future impact imposed by NASH-related HCC.

Cholankeril G, Patel R, Khurana S, Satapathy SK. Hepatocellular carcinoma in non-alcoholic steatohepatitis: Current knowledge and implications for management. *World J Hepatol* 2017; 9(11): 533-543 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i11/533.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i11.533

INTRODUCTION

Hepatocellular carcinoma (HCC) accounts for 90% of primary liver cancers Worldwide, HCC being the sixth most common cancer, and is the second leading cause of cancer-related death[1]. HCC largely occurs in the background of chronic liver disease and cirrhosis of the liver[2]. The leading liver disease etiologies for cirrhosis in patients with HCC include but are not limited to chronic hepatitis B, chronic hepatitis C virus (HCV), and alcoholic liver disease. With advent of curative treatments for HCV, the risk of progression to cirrhosis and development of HCC secondary to HCV is anticipated to decline. However, in recent years, non-alcoholic fatty liver disease (NAFLD) has quickly risen as one of leading etiologies for liver disease. NAFLD is a spectrum of chronic liver disease ranging from simple hepatic steatosis to liver cell injury and inflammation known as non-alcoholic steatohepatitis (NASH). The rising incidence of NAFLD/NASH has subsequently led to a dramatic rise in NASH-related HCC incidence[3]. Numerous studies have demonstrated that NASH can lead to advanced fibrosis and cirrhosis, thereby increasing the risk of developing HCC[4-6]. Among patients with NAFLD or NASH, liver disease is the third leading cause of death[4], while HCC represents the main cause of death in this group[7]. The cumulative annual incidence rate for developing HCC in patients with NASH-related cirrhosis is approximately 2.4%-12.8%[8]. In the absence of NASH or cirrhosis, NAFLD can present with HCC. These patients usually present with less aggressive tumors and are less likely to diagnosed by surveillance compared to HCC that develops in the setting of viral hepatitis[9-11]. A similar rising trend has been reported in NASH progressing to HCC in the absence of cirrhosis[12-14]. In NASH, several risk factors for HCC development have been identified including metabolic syndrome and insulin resistance causing changes in serum cytokines, persistent inflammation, and altered gut microflora and bile composition[15].

EPIDEMIOLOGY

Currently, NAFLD affects more than 80 million Americans, making it the most common etiology for liver disease in the United States. With the incidence of obesity, diabetes and metabolic syndrome continuing to increase in the United States and Europe, NAFLD/NASH may become the most common cause of HCC in developed countries in the near future[16]. In 2012, primary liver cancer was recognized overall as the second most common cause of cancer-related death in the world. In the United States, HCC is the most rapidly rising cause of cancer and cancer-related deaths with an incidence that has tripled over the last decade. This high likelihood for mortality reflects a poor prognosis without therapeutic intervention[17]. HCC is the most prevalent histological subtype accounting for 70%-85% of primary liver malignancies[18]. Compared to HCC in alcoholic liver disease and viral hepatitis, there is a lack of strong epidemiological data regarding the incidence and prevalence of HCC in NAFLD[19]. While the prevalence of NAFLD is thought to be highest among Hispanics and Caucasians, the ethnic distribution among NAFLD/NASH-related HCC patients has yet to be defined[20]. NASH-related HCC patients are predominantly male; however, gender has not been proven to be a statistical risk factor NASH progression to HCC[21]. Studies analyzing demographic and clinical characteristics of NASH-related HCC patients are outlined in Table 1. Reports indicate that NASH can be verified by histological evaluation in up to 47% of all NAFLD cases among obese individuals[22,23]. Amongst a growing population of diabetes which has surpassed 26 million in the United States, the prevalence of biopsy-proven NAFLD and NASH has been reported to be as high as 74% and 11%, respectively[24,25].

This rise in the incidence of NASH-related HCC has impacted trends in liver transplantation as well. A retrospective cohort study amongst adult liver transplant recipients from 2002-2012 indicated that there was 4-fold increase in patients undergoing liver transplant for NASH-related HCC compared to 2-fold increase in number of patients undergoing transplantation for HCV-related HCC[26]. During this 10-year span, NASH also became the second leading cause of HCC-related liver transplantation in America, steadily increasing from 8.3% in 2002 to 10.3% in 2007 and to 13.5% in 2012[16], and most likely will surpass 15% by 2017.

PROGRESSION OF NASH/NAFLD TO HCC

NAFLD is the hepatic manifestation of metabolic syndrome, with insulin resistance driving the alteration in physiology. As mentioned earlier, it ranges from isolated hepatic steatosis, to NASH with or without cirrhosis, and progression to HCC. The diagnosis of NASH is based on histological evidence of hepatic steatosis or magnetic resonance spectroscopic evidence > 5% fat accumulation of liver weight without the presence of secondary causes

Table 1 Reported studies of hepatocellular carcinoma in patients with cirrhotic and non-cirrhotic non-alcoholic fatty liver disease/non-alcoholic steatohepatitis, and their clinical characteristics

Ref.	All (*n*)	NASH/NAFLD (*n*)	Study type	Clinical characteristics	Cirrhotic NASH with HCC		Non-cirrhotic NASH with HCC	
					Histological diagnosis	Clinical diagnosis	Histological diagnosis	Clinical diagnosis
Cotrim *et al*[97]	110	110	Cohort	Age, 67 ± 11 yr; male, 72 (65.5%); non-Hispanic white, N/A	32 (29.1%)	58 (52.7%)	20 (18.2%)	0
Van Meer *et al*[98]	933	91[1]	Cohort	Age, 64 yr; male, 60 (66%); non-Hispanic white, N/A	N/A	N/A	91 (100%)	N/A
Shrager *et al*[99]	9	9	Case series	Age, 58 yr; male, 8 (88.9%); non-Hispanic white, N/A	5 (55.5%)	N/A	4 (44.4%)	N/A
Kikuchi *et al*[93]	42	38	Case series	Age, 66.5 yr; male 26 (62%); non-Hispanic white, N/A	34	N/A	4	N/A
Chagas *et al*[100]	394	7	Prospectiv	Age, 63 ± 13 yr; Male 4 (57%); non-Hispanic white, N/A	6	N/A	1	N/A
Ertle *et al*[101]	150	36	Cohort	Age, 68.6 ± 8.4 yr; male 32 (88.9%); non-Hispanic white, N/A	5	14[2]	10	7[2]
Tokushige *et al*[102]	2299	292	Cohort	Age, 72 ± 8.4 yr; male, 181 (62%)	181[3]	N/A	111[3]	N/A
Hashizume *et al*[103]	1310	10	Case series	Age 71.5 yr; male 6 (66.7%)	5	N/A	4	N/A
Kawada *et al*[13]	807	8	Cohort	Age 73 yr; male 3/6 (50%); non-Hispanic white, N/A	2	N/A	6	N/A
Malik *et al*[104]	143	143	Case control	Age 59 ± 7.6 yr; male 44 (44.9%); 16 non-Hispanic White, 1 Asian	17	N/A	0	N/A
Takuma *et al*[105]	11	11	Case series/ Literature review	Age 73.8 ± 4.9 yr; male 5 (45%)	4	N/A	7	N/A
Perumpail *et al*[106]	44	6	Cohort	Age 72 ± 8 yr; male 5 (83.3%)	NA	NA	6	N/A
Ascha *et al*[107]	510	195	Cohort	Age 56.5 yr; male 86 (44.1%)	NA	NA	N/A	25[4]
Mohamad *et al*[108]	83	83	Cohort retrospective	Age 64.8 ± 10.4 yr; male 54 (65.1%); non-Hispanic White, 77 (92.8%)	47	N/A	36	N/A

[1]Histological data available in 86 patients only; [2]AASLD Radiological criteria used for diagnosis; [3]Results based on both liver biopsy and abdominal imaging. Differentiating data not available in the study; [4]Histologic confirmation obtained in 59% of the patients diagnosed with HCC. HCC: Hepatocellular carcinoma; EMT: Epithelial to mesenchymal transition; NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; N/A: Not available.

such as alcohol abuse, endocrine disorders, chronic HCV infection or familial hypobetalipoproteinemia[27]. Recent evidence has demonstrated an association between NASH and HCC to be exclusive to patients who had progressed to cirrhosis, suggesting causality[8].

Compared to benign course of simple steatosis, patients with NASH are more likely to develop progressive advanced liver disease. Matteoni *et al*[28] demonstrated increased rates of cirrhosis in patients with NASH compared to those with fatty liver without NASH (25% *vs* 3%, respectively), and increased risk of liver disease-related death (11% *vs* 2%, respectively). In a much larger study across the entire spectrum of NAFLD which included 420 patients, Rafiq *et al*[29] demonstrated a higher mortality in those with NASH/NAFLD when compared to the general population; liver-related deaths occurred in 13% *vs* < 1% in general population, and 3% of those with NAFLD developed cirrhosis. Another study further confirmed increased rate of liver-related deaths among patients with NASH when compared with those without NASH (17.5% *vs* 3%, respectively). In patients with compensated cirrhosis, NASH-related cirrhosis patients had better survival outcomes compared to HCV-related cirrhosis patients. However, in decompensated cirrhosis both cohorts had comparable poor outcomes[30,31]. Currently, both the American Association for the Study of Liver Diseases, and the European Association for the Study of Liver Disease recommend screening for HCC in patients with NASH related cirrhosis every 6-12 mo[32].

HCC IN NON-CIRRHOTIC NAFLD/NASH

Emerging evidence suggests that a significant proportion of patients with NAFLD-associated HCC, do not have

histologic evidence of cirrhosis. In a study conducted by Kawada *et al*[13], of 1168 patients who underwent hepatic resection for HCC, 6 of 8 patients with NASH-related HCC did not demonstrate cirrhosis. This study suggested that the presence of cirrhosis in NASH-related HCC was lower compared to HCV-related HCC. These data suggest that compared to patients HCV, HCC may develop at an earlier stage those with NASH. Paradis *et al*[33] analyzed 128 HCC patients who were recruited over 12 years, and reported significant number of patients with NASH developed HCC in the absence of fibrosis when compared to HCC in the setting of other underlying chronic liver disease (65% with F0-F2 in NASH group *vs* 26% in chronic liver disease)[33,34]. To explain this phenomenon in non-cirrhotic NAFLD patients, one proposed hypothesis is the malignant transformation of hepatic adenoma. Few published reports have suggested that in the presence of metabolic syndrome, hepatocellular adenoma may incur a malignant transformation[19,35].

HCC IN CIRRHOTIC NAFLD/NASH

During the last two decades, various studies have tried to determine the relationship between NAFLD/NASH, cryptogenic cirrhosis and HCC. A recent meta-analyses by White *et al*[8] showed that approximately 60% HCC cases attributed to NAFLD/NASH had cirrhosis either before or at the time of diagnosis. This meta analyses also included review of cohort and longitudinal studies which showed that NASH-associated cirrhosis consistently carried an increased HCC risk ranging between 2.4% and 12.8%[8]. Additionally, this study reported the risk of developing HCC is lower in patients with cirrhosis due to NAFLD/NASH when compared to those with chronic HCV (NAFLD/NASH, 26.9% *vs* HCV, 19.7%).

The true prevalence of NASH and NASH-related HCC is likely underestimated. In up to 6.9%-29% of HCC, the underlying etiology of liver disease is unknown and is considered secondary to cryptogenic cirrhosis[19]. Features suggestive of NASH are more frequently observed in HCC arising in patients with cryptogenic cirrhosis than in age- and sex-matched HCC patients of well-defined viral or alcoholic etiology[36]. Although the prevalence of NAFLD/NASH-related HCC is not well defined, the increasing incidence of obesity and diabetes, suggests the impact of NAFLD/NASH-related HCC will continue to grow.

MORTALITY IN NAFLD/NASH

Long term outcomes in NAFLD and NASH has been evaluated in several studies and distinctive differences between NASH and non-NASH subtypes of NAFLD have been shown[28,29,37-42]. Type 2 diabetes mellitus has been shown to increase the risk of both liver- related mortality and overall mortality in NAFLD patients[43,44]. In light of these findings NAFLD patients with type Ⅱ diabetes should be prioritized in future treatment protocols[44]. A population-based study published in 1996 followed 153852 subjects and found that diabetic patients had a standardized incidence ratio of 4.1 for HCC[45]. However, another retrospective analysis from United States Veteran Registry noted increased the risk of primary liver cancer in patients with diabetes only in the presence of other risk factors such as hepatitis C or B or alcoholic cirrhosis[46]. These observations were not supported by further analysis that found an incremented HCC risk in diabetic patients independently from alcoholic liver disease and viral hepatitis[47,48]. In a recent meta-analyses, Younossi *et al*[49] reported that in NAFLD patients, annual incidence of HCC was 0.44 per 1000 person-years (95%CI: 0.29-0.66), whereas for those with NASH, the annual HCC incident rate was 5.29 per 1000 person-years (95%CI: 0.75-37.56). Among NAFLD cohort, the pooled liver-specific and overall mortality incidence rates were 0.77 per 1000 person-years (95%CI: 0.33-1.77 events) and 15.44 per 1000 person-years (95%CI: 11.72-20.34 events), respectively. Among the NASH cohort, the pooled liver-specific and overall mortality incidence rates were 11.77 per 1000 person-years (95%CI: 7.10-19.53 events) and 25.56 per 1000 person-years (95%CI: 6.29-103.8 events), respectively.

Although cardio-vascular (CV) events remain the major cause of death in patients with NAFLD and NASH, the CV mortality rate amongst the NASH and non-NASH subtypes of NAFLD is similar[42,50-52]. Since patients with NASH have significantly higher liver-related mortality than those with non-NASH NAFLD, treatment strategies should be designed to ameliorate the risks for cardiovascular mortality[28,29,38,40-42,49,50]. Further, patients with NASH and type 2 diabetes mellitus, will need increased attention and linkage of care to reduce liver disease-related compliactions and to reduce their risk of HCC[53-55].

RISK FACTORS AND PROPOSED MECHANISMS FOR NASH-RELATED HCC

Development of HCC in the setting of chronic liver disease is a complex but gradual process that requires transition through a dysplasia-carcinoma sequence. Several putative oncogenic mechanisms has been incriminated that lead to genomic instability, including telomere erosion, chromosome segregation defects and alterations in the DNA-damage-response pathways[56,57]. Obesity and diabetes are involved in the mechanisms involved in the development of HCC in NAFLD. The development of HCC in NAFLD is likely multifactorial; involving low grade chronic systemic inflammatory response, increased lipid storage and lipotoxicity, gut disbiosis with elevated levels of lipopolysaccharide (LPS) and hyperinsulinemia with insulin resistance and increased IGF levels[19]. In addition patients with HCC from NAFLD in general has a distinctive phenotype with presentation in older age, being less aggressive and less likely to be diagnosed by surveillance compared with HCC caused by viral hepatitis[9-11]. Other factors such as genetic polymorphism and, increased iron absorption may also lead to development of HCC in NASH[14]. Proposed mechanisms for NASH-related HCC are depicted in Figure 1.

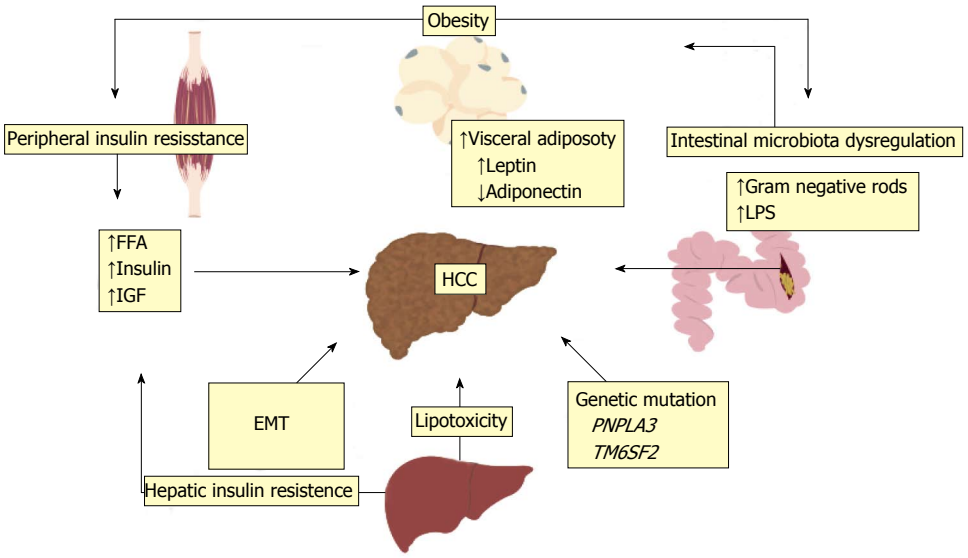

Figure 1 Risk factors and proposed mechanisms for non-alcoholic fatty liver disease and non-alcoholic steatohepatitis-related hepatocellular carcinoma. The development of NAFLD and NASH-related HCC is multifactorial. Proposed pathogenic mechanisms include obesity, peripheral and hepatic insulin resistance from type 2 diabetes, increased hepatic lipid storage and lipotoxicity, EMT, genetic mutations and intestinal mibrobiota dysregulation. HCC: Hepatocellular carcinoma; EMT: Epithelial to mesenchymal transition; NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; FFA: Free fatty acid; IGF: Insulin-like growth factor; LPS: Lipopolysaccharide; *PNPLA3*: Patatin-like phospholipase domain-containing 3; *TM6SF2*: Transmembrane 6 superfamily member 2.

Cytokines carry out the intercellular communication signals, cellular interactions along with growth and differentiation. Disease states cause imbalances in cytokine levels promoting aberrant signaling and modulating inflammatory responses seen in epithelial to mesenchymal transition pathologic process[15]. Imbalances in the levels of cytokines such as tumor necrosis factor (TNF)-alpha, leptin, adiponectin and interleukin-6 (IL-6) play a pivotal role in NASH[58-60].

Obesity

Obesity is a significant risk for the development of HCC particularly in patients with NASH, who have a higher predisposition for obesity. Obese (body mass index > 30 kg/m^2) patients have a reported 1.93-fold higher risk of developing primary liver cancer. Obesity and excessive visceral adipose tissue has been associated with a chronic inflammatory state due to increased levels of leptin. Leptin, a profibrotic and proangiogenic cytokine, activates the Janus kinase (JAK) pathway, thereby initiating an intracellular signaling cascade of pro-inflammatory cytokines[61,62]. Obesity has also been associated reduced level of adiponectin, an anti-inflammatory cytokine. Additionally, obesity has been associated with other risk factors including insulin resistance, increased hepatic lipid storage and alteration of intestinal microflora.

Insulin resistance

Diabetes has shown to be an independent risk factor for the development of HCC in NASH[61,63]. Excessive fat accumulation and obesity lead to hepatic and peripheral insulin resistance causing compensatory hyperinsulinemia. Evidence supports that insulin and insulin-like growth factor (IGF) may promote the development of primary liver cancer by activating various oncogenic pathways[61]. Both IGF-1 and insulin receptor substrate stimulates growth by activating the mitogen-activate protein kinase (MAPK) pathway and increases the transcription of c-fos and c-jun, known proto-oncogenes. Activation of MAPK pathway subsequently activates the Wnt/β-catenin signaling cascade leading to fibrosis and hepatocarcinogenesis[61,62].

Lipotoxicity

Increased lipid accumulation in the liver arises from lipolysis within peripheral adipose tissue, dietary sources and de novo hepatic lipogenesis[19,64]. This increased lipid accumulation causes hepatic lipotoxicity resulting in the excessive production of saturated and monounsaturated free fatty acids (FFAs)[65]. These FFAs undergo β-oxidation leading to formation of reactive oxygen species. Reactive oxygen species induce endothelial reticulum stress, mitochondrial damage and gene transcription promoting inflammatory cell signaling pathways.

Intestinal microflora dysregulation

Other novel pathogenic pathway between the gut and liver has been demonstrated, which is driven by dietary changes leading to gut dysbiosis that has the potential to generate hepatic inflammation can ultimately influence HCC. In NASH patients, small intestinal bacterial overgrowth[66,67] and increased TNF-α levels, elevated expression of Toll-like receptor (TLR) 4 and increased levels of serum IL-8[67] has been demonstrated.

LPS, a major component of outer membrane of gram-negative bacteria, is an endotoxin that causes inflammation upon entering the systemic circulation. The involvement of LPS in the development of HCC is sus-

pected by the observation that LPS removal by gut sterilization results in diminished tumor growth in patients with chronic liver injury[68,69]. In two recent studies, the investigators observed in NASH patients, increased levels of TNF-alpha, interleukin-8 and elevated expression of TLR 4 and small intestinal bacterial overgrowth[66,67]. NASH patients also have less gut gram-negative *Bacteroidetes* and an increase in alcohol producing bacteria when compared to patients with simple steatosis, which raises a question as to whether these strains are involved in the pathogenesis of NASH[70,71].

Several recent studies have identified potential link between gut dysbiosis and NAFLD in both in animal models and human[66-72]. There is incremental evidence for gut microbiome in the pathogenesis of NASH based on these findings, suggesting potential therapeutic role of correcting of gut dysbiosis to a more healthy phenotype in limiting progression of NASH. Evidence linking gut microbiota, NASH, and HCC development is reported from Dapito *et al*[69]. They treated mice with diethylnitrosamine (DEN) followed by carbon tetrachloride (CCL4) to promote fibrosis-driven HCC[69]. They found that TLR4-deficient mice had limited HCC growth; DEN/CCL4-treated wild-type mice that received antibiotics also had reduced tumor growth, suggesting that the microbiota played a role in HCC progression possibly *via* LPS-TLR4 axis.

Gut microbiota can catalyse generation of secondary bile acids such a sDCA, which is known to induce DNA damage[72]. Yoshimoto *et al*[68] found that DCA can promote the activation of a senescence-associated secretory phenotype in HSCs, reflected by the secretion of IL-1β. Further they observed limited obesity-induced HCC development in the absence of IL-1β, and alleviation of HCC development with antibiotic treatment. In addition, lowering of DCA or feeding of DCA, limited or enhanced HCC growth respectively. Although the role for bile acids in NASH HCC progression need further exploration, these studies certainly lay the foundation for future exploratory studies in both animal models and human.

Genetic polymorphisms

Genetic polymorphism is also one of the factors that may account for development of HCC in NAFLD. Genetic predisposition plays an important role in susceptibility to the metabolic syndrome and NASH. Recent genome-wide association studies have identified a single nucleotide polymorphism in the patatin-like phospholipase domain-containing 3 *(PNPLA3)* gene. Specifically, a C-to-G genotype in the *rs738409* gene, encoding the I148M protein variant, determines differences in hepatic fat accumulation[73]. Although the physiological and biological functions of *PNPLA3* within the liver, which effect fat accumulation and NASH, remain unclear, the association of *rs738409* polymorphisms with HCC is evident[74].

It has also been suggested a polymorphism in the transmembrane 6 superfamily member 2 gene *(TM6SF2)* may increase the risk of NASH progression to HCC[75]. *TM6SF2* mutation encodes for a loss of function substitution of lysine to glutamic acid. This *TM6SF2* variant was associated with liver injury in NAFLD and NASH patients. While there is an increased prevalence of the *TM6SF2* variant in NAFLD and NASH patients, conflicting preliminary data exists regarding its role in the progression to HCC.

Other risk factors

Increased intrahepatic iron accumulation has been associated with NASH progression to HCC. Although clinical data is limited, Sorrentino *et al*[76] demonstrated higher hepatic iron storage levels among NASH-related HCC patients compared to NASH patients. The underlying mechanism of increased iron absorption in NASH patients may be related to oxidative DNA damage but further studies are required to understand the role of iron accumulation in NAFLD and HCC[19,76].

Other significant risk factors for NASH progression to HCC include advanced age and concomitant chronic alcohol consumption[77]. Alcohol consumption among NASH patients has an associated 3.6-fold increased risk for development of HCC. Also emerging evidence has suggested a possible correlation between obstructive sleep apnea and NAFLD and NASH but its association to development of HCC has not been investigated[78].

SURVEILLANCE

With the increasing prevalence of NAFLD/NASH and associated HCC, chemopreventive and perhaps reconsideration of current surveillance guidelines are needed[16]. The current AASLD guidelines recommend screening for HCC every 6 mo in patients with cirrhosis. However, the current guidelines lack recommendations for surveillance of NASH patients without cirrhosis who are at risk for developing HCC. This is further supported by a study performed by Mittal *et al*[79] in which the data collected on about 1500 HCC patients where HCC related to NASH received less surveillance and treatment compared with HCC arising in underlying etiologies related to HCV and alcohol.

The lack of longitudinal data in the non-cirrhotic NASH population makes it difficult to develop good evidence - based screening guideline. There is a need for studies addressing the screening guidelines for surveillance of HCC in NASH particularly for non-cirrhotic individuals. We suspect that earlier screening may be needed in patients with NASH who have multiple risk factors for HCC[19].

CURRENT THERAPEUTIC OPTIONS

The biological heterogeneity of HCC makes it difficult to clarify the key mechanisms of cancer development and thus to develop and implement effective therapies[80]. A few chemopreventive agents have shown promise in the prevention and treatment of steatohepatitis and fibrosis; however these are small individual studies and thus there is a lack of a general consensus due to paucity

of data. There is currently no effective chemoprevention to decrease the incidence of HCC. Exceptions include nucleoside analogues used to reduce viral replication in those with hepatitis B, and DAAs for HCV which have very high cure rates[81].

Medical therapy

Regular exercise and controlled caloric intake is the mainstay of therapy for NAFLD, however the extent to which these are effective to prevent the development of HCC is unclear. Physical activity has been reported to have a preventive effect on development of HCC. A large prospective cohort study, which included over 400000 participants suggested that increased physical activity might have a role in HCC prevention that is independent of weight reduction[82]. Preliminary data suggests that statins, metformin and S-Adenosylmethonine are potential chemopreventive agents[16].

Patients with NASH have been found to be deficient in vitamin E and D; vitamin D deficiency is thought to play a role in hepatic carcinogenesis[83,84]. Other dietary antioxidants such as vitamin C, selenium, coenzyme Q12 and certain phytochemicals have also been touted have chemopreventive potential[85]. NASH patients have been shown to have low levels of serum lycopene[83]. There is a strong inverse relationship between serum lycopene levels and the risk of GI cancers[86].

Metformin has an antitumor effect in HCC *via* suppression of mTOR pathway[87]. Although it may not have a role in the treatment of NASH, metformin may have a role in decreasing the incidence of HCC in NASH[16]. A review of two recent meta-analyses included 22650 cases of HCC in approximately 334000 patients with type 2 diabetes revealed that metformin reduced incidence of HCC by 50% whereas sulfonylurea and insulin increased incidence of HCC by 62% and 161% respectively[88]. The use of metformin has also been shown to increase survival of HCC patients who have cirrhosis[89].

Statins have shown a protective effect in individuals who are at risk for development of steatohepatiits and F2-F4 fibrosis[90]. The protective effect of statins in diabetics is thought to be due to anti-inflammatory properties of statins mediated through the inhibition of JAK[91]. A recent Swedish case control study which evaluated almost 4000 HCC patients treated with statin that were matched with 19970 controls showed that the odds ratio for HCC amongst statin users was 0.88, suggesting a modest but beneficial effect of statins in reducing the risk of HCC[92].

The heterogeneity of HCC makes it difficult to clarify the mechanism of cancer development and to develop effective therapeutics. However, an integrative functional genomics approach will contribute to the discovery of potential molecular features critical for HCC development. These studies will provide us with better treatment strategies that may be effective to treat all HCC patients including those with NASH.

Surgical therapy

Curative treatment options including liver resection and liver transplantation in select early-stage HCC candidates. The Barcelona Clinic Liver Cancer staging system and therapeutic algorithm has been applied to HCC candidates including those with NASH-related HCC[93]. Non-cirrhotic NASH-related HCC patients who underwent curative surgical resection have shown to have superior survival than those with HCV and alcohol-related HCC[11].

Since the implementation of the Model for End-Stage Liver Disease (MELD) system for liver allocation in 2002 the number of HCC liver transplantations has dramatically increased. In 2012, they accounted for 23.2% of all liver transplantations in the United States[26]. HCC liver candidates are eligible to receive a MELD exception which upgrades their priority and thus, increases their likelihood of receiving liver transplant and survival. Subsequently, a higher number of HCC candidates have sought listing for liver transplant. A recent study using United Network for Organ Sharing data from 2004-2013[94] demonstrated that NASH-related HCC candidates have lower rates for receiving MELD exception and have longer time to transplant compared to HCV-related HCC. Despite this, NASH-related HCC was the fastest growing indication for liver transplantation from 2002-2012[26]. NASH-related HCC liver transplant recipients have better outcomes compared HCV-related HCC with a 5-year post-transplant survival approaching 68%[95]. NASH-related HCC liver transplant recipients with morbid obesity and CV risk factors tend to have poorer outcomes[96]. Further research is needed to evaluate NASH-related HCC post liver transplant survival risk factors and exploring why this growing cohort is less likely to receive a MELD exception.

CONCLUSION

With the prevalence of HCV expected to decline, NASH is anticipated to account for a greater proportion of HCC incidence in the near future due to the growing epidemic of obesity and diabetes. The annual incidence rate of developing HCC in patients with NASH-related cirrhosis is not clearly understood with rates ranging from 2.6%-12.8%. Recent evidence has shown a significant proportion of patients with NAFLD and NASH progress to HCC in the absence of cirrhosis. While liver resection and transplantation represent curative therapeutic options in select NASH-related HCC candidates, they also have placed a significant burden to our healthcare resources and utilization. Currently NASH-related HCC is the fastest growing indication for liver transplant in HCC candidates. Increased efforts to implement effective screening and preventative strategies, particularly in non-cirrhotic NASH cohort, are needed to reduce the future impact imposed by NASH and NASH-related HCC.

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ORIGINAL ARTICLE

Retrospective Study

Efficacy and safety of dual therapy with daclatasvir and asunaprevir in elderly patients

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Abstract

AIM

To survey the efficacy and safety of dual therapy with daclatasvir and asunaprevir in the elderly hepatitis C virus (HCV) patients multicentricity.

METHODS

Interferon-ineligible/intolerant patients and non-responders to previous pegylated-interferon/ribavirin therapy with chronic HCV genotype 1b infection were enrolled. Child B, C cirrhotic patients were excluded.

Patients received oral direct acting antiviral treatment consisting of 60 mg daclatasvir once daily plus 200 mg asunaprevir twice daily for 24 wk. We divided the patients into two groups of 56 elderly patients (≥ 75 years-old) and 141 non-elderly patients (< 75 years old) and compared the efficacy and safety.

RESULTS

Ninety-one point one percent of elderly patients and 90.1% of non-elderly patients achieved sustained virological response at 24 wk (SVR_{24}). In the former, 1.8% experienced viral breakthrough, as compared with 3.5% in the latter (not significant). Adverse events occurred in 55.4% of the former and 56.0% of the latter. In the former, 7 cases (12.5%) were discontinued due to adverse events, and in the latter 9 cases were discontinued (6.4%, not significant).

CONCLUSION

Dual therapy with daclatasvir and asunaprevir achieved the same high rates of SVR_{24} in HCV elderly patients without more adverse events than in the non-elderly patients.

Key words: Asunaprevir; Chronic hepatitis; Daclatasvir; Dual oral therapy; Elderly patients; Hepatitis C virus infection; Hepatitis C virus; Liver cirrhosis

Core tip: Recently, it was demonstrated that dual oral therapy with daclatasvir and asunaprevir without pegylated-interferon/ribavirin was well tolerated and achieved high sustained virological response rates in Japanese patients with chronic hepatitis C virus genotype Ib infection, including patients with liver cirrhosis (Child A stage). However, the efficacy and side effects of these drugs was previously studied in non-elderly patients (less than 70 years of age). Those in elderly patients, who are supposed to have higher incidence of hepatocellular carcinoma, have not been studied. We demonstrated that efficacy and side effects in elderly patients were nearly the same as in non-elderly patients.

Tarao K, Tanaka K, Nozaki A, Sato A, Ishii T, Komatsu H, Ikeda T, Komatsu T, Matsushima S, Oshige K. Efficacy and safety of dual therapy with daclatasvir and asunaprevir in elderly patients. *World J Hepatol* 2017; 9(11): 544-550 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i11/544.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i11.544

INTRODUCTION

Recently, it was demonstrated that dual oral therapy with daclatasvir and asunaprevir without pegylated-interferon/ribavirin (PegIFNα/RBV) was well tolerated and achieved high sustained virological response (SVR) rates in difficult-to-treat Japanese patients with chronic hepatitis C virus (HCV) genotype Ib infection, including patients with liver cirrhosis (Child A stage)[1-4].

It is generally accepted that the average age of the patients with HCV-associated liver disease in Japan is increasing, and indeed patients more than 60 years of age represent more than 70% of all patients[5]. Moreover, Kumada *et al*[6] recently analyzed the age distribution of 3388 persistent HCV-infected patients and found that the median age was 70 years, and 2249 (66.4%) were elderly patients of more than 65 years.

Also, recently, Asahina *et al*[7] demonstrated that the risk for hepatocellular carcinoma (HCC) after interferon treatment was age-dependent and increased predominantly when the age at primary liver biopsy was > 65 years. They also demonstrated that progression of fibrosis over time was significantly accelerated in older patients. In addition, elderly patients with HCV-associated chronic hepatitis are thought to develop liver cirrhosis more rapidly, and HCC might develop more frequently as a result. An increase in the aged population is an impending problem, and we must eradicate the HCV infection as soon as possible in elderly patients.

We therefore retrospectively examined the efficacy and safety of dual therapy with the nonstructural protein 5A inhibitor, daclatasvir, and the nonstructural protein 3 protein inhibitor, asunaprevir, in elderly patients (≥ 75 years of age) with hepatitis C chronic hepatitis or liver cirrhosis (Child A stage), who may have suffered from longer periods of HCV infection, in many large hospitals in Kanagawa Prefecture in Japan.

MATERIALS AND METHODS

Study design

This study included two populations of patients with HCV genotype 1b infection: Null responders (< 2 $\log_{10}$ decline in serum HCV RNA levels after 12 wk of prior PegIFNα/RBV), and PegIFNα/RBV ineligible/intolerant patients. The latter group was either patients who discontinued prior therapy with PegIFNα/RBV due to intolerance after < 12 wk, or patients who were treatment-naïve but poor candidates for PegIFN-α/RBV for medical reasons such as advanced age or complications of depression, anemia, myelosuppression, diabetes or cardiovascular or renal dysfunction. Of the cirrhotic patients, only those with Child-Pugh stage A were enrolled[8], and patients with Child-Pugh stages B and C were omitted.

The patients were out-patients and visited the following hospitals in Kanagawa Prefecture of Japan between 1 September 2014 and 30 March 2015: Tarao's Gastroenterological Clinic, Yokohama City University Medical Center, Yokohama Seibu Hospital of St. Marianna University, Yokohama Municipal Citizens Hospital, Yokosuka General Hospital Uwamachi, and National Hospital Organization Yokohama Medical Center.

Elderly patients were defined as those equal to or over 75 years old. Enrolled patients were divided into

Table 1 Background of elderly (≥ 75 years old) and non-elderly (< 75 years old) patients

Parameter	Elderly patients, *n* = 56	Non-elderly patients, *n* = 141	*P*
Cirrhosis/chronic hepatitis	30/26	44/97	0.003
Age in years	77.8 (75-83)	65.3 (34-74)	
Male/female	23/33 (41.1%/58.9%)	54/87 (38.3%/61.7%)	
HCV genotype 1b, %	100	100	
HCV RNA, mean $\log_{10}$ IU/mL	5.85 ± 0.77	6.12 ± 0.70	
Pegylated-interferon/ribavirin non-responder, %	17.9	25.5	0.251

HCV: Hepatitis C virus.

two groups, elderly patients (≥ 75 years old) and non-elderly patients (< 75 years old), and efficacy and safety assessments were compared. The primary efficacy end-point was the proportion of patients with undetectable HCV RNA at 24 wk post-treatment (SVR_{24}).

Written informed consent was obtained from all patients. The study was approved by institutional review boards in each hospital and conducted in compliance with the Declaration of Helsinki.

Patients

Eligible patients were men and women, aged 34-83 years, with HCV genotype 1 infection with chronic hepatitis or compensated liver cirrhosis. Patients with cirrhosis were confined to Child-Pugh stage A[8], and patients with stage B and C cirrhosis were excluded. Exclusionary laboratory findings included alanine aminotransferase (ALT) > 5 × upper limit of normal (ULN), total bilirubin > 2 mg/dL, albumin < 3.5 g/dL, hemoglobin < 9.0 g/dL, white blood cells < 1500 mm^3, platelets < 50000/mm^3, and creatinine > 1.8 × ULN. No patients had prior exposure to HCV direct-acting antivirals.

Analysis of resistant-associated variants

At prc-treatment points and the resistant-associated variants (RAVs) in NS5A (Y93H) were investigated by PCR-invader assay. PCR-invader assays were conducted by BML Inc. (Saitama, Japan), and weakly positive and negative samples were defined as substitution-negative. In 132 out of 197 cases, the RAVs was examined and the results were as follows: Y93H ≤ 1% in 116 cases (87.9%), 2%-5% in 14 cases (10.6%), 23% in 1 case (7.6%), 64% in 1 case (7.6%).

Study drug dosing

Patients received 24 wk of treatment with 60 mg daclatasvir once daily combined with 200 mg asunaprevir twice daily, and participated in 24 wk of post-treatment follow-up. HCV RNA, physical examinations, adverse events, laboratory parameters and concomitant medications were assessed at day 1 (baseline), treatment weeks 1, 2, 3, 4, 6, 8, 10, 12, 16, 20 and 24, and post-treatment weeks 4, 8, 12 and 24.

Statistical analysis

Pearson's χ^2 test and the Student's *t*-test were used for statistical analyses. Statistical significance was considered to exist at $P < 0.05$.

RESULTS

A total of 197 patients were enrolled in this retrospective study, and included 56 elderly patients and 141 non-elderly patients. Backgrounds of the patients are shown in Table 1. In the elderly patients, the number of cirrhotic patients (53.6%) was significantly larger, as compared with 31.2% in the non-elderly patients ($P = 0.003$). The average age was 77.8 years in the elderly patients and 65.3 years in the non-elderly patients. The male/female ratio was nearly the same in the two groups ($P = 0.719$). HCV genotype was 1b in all patients. HCV RNA (mean $\log_{10}$ IU/mL) was 5.85 ± 0.77 in the former and 6.12 ± 0.70 in the latter ($P = 0.016$). Percentages of the non-responder patients in the prior PegIFNα/RBV therapy group were 17.9% in the former and 25.5% in the latter ($P = 0.251$).

Virologic outcomes

Of the elderly patients, 51 (91.1%) achieved SVR_{24}, while in the non-elderly patients, 127 (90.1%) achieved SVR_{24}. The ratio of patients achieving SVR_{24} was nearly the same in the two groups (Table 2). The ratio of patients who achieved SVR_{24} in the group that discontinued due to side effects was 71.4% (5/7) for the elderly and 77.8% (7/9) for the non-elderly patients (Table 2).

Viral breakthrough

Only one patient out of 56 (1.8%) experienced viral breakthrough in the elderly group, as compared with 5 out of 141 (3.5%) in the non-elderly group (not significant, $P = 0.519$). Post-treatment relapse was seen in 2 (3.6%) of the elderly patients, as compared with 7 (5.0%) of the non-elderly patients (not significant, $P = 0.675$) (Table 2).

Safety

Adverse events and laboratory abnormalities in each group are shown in Table 3. There were no significant differences in each event between elderly and non-elderly groups. The total number of patients who showed adverse events in the elderly group was 31 out of 56 (55.4%), which was nearly the same in the non-elderly group (79 out of 141, 56.0%) (Table 4).

Table 5 shows the causes of discontinuation and

Table 2 Virologic outcomes

Parameter	Elderly patients, *n* = 56	Non-elderly patients, *n* = 141	*P*
SVR_{24}	51 (91.1)	127 (90.1)	
Viral breakthrough	1 (1.8)	5 (3.5)	0.519
Post-treatment relapse	2 (3.6)	7 (5.0)	0.675
Ratio of patients who achieved SVR_{24} in the discontinued cases due to side effects	5/7 (71.4)	7/9 (77.8)	

Data are presented as *n* (%). SVR_{24}: Sustained virological response at 24-wk.

Table 3 Adverse events and laboratory abnormalities

Event	Elderly patients, *n* = 56	Non-elderly patients, *n* = 141
Nasopharyngitis	5 (8.9)	6 (4.3)
Headache	4 (7.1)	9 (6.4)
Diarrhea	3 (5.4)	5 (3.5)
Pyrexia	2 (3.6)	12 (8.5)
Malaise	7 (12.5)	8 (5.7)
Anorexia	6 (10.7)	8 (5.7)
AST elevation	15 (26.8)	55 (39.0)
ALT elevation	14 (25.0)	54 (38.3)
Hb decrease	8 (14.3)	11 (7.8)
Total bilirubin increase	2 (3.6)	11 (7.8)
Creatinine increase	8 (14.3)	13 (9.2)

Data are presented as *n* (%). ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; Hb: Hemoglobin.

Table 4 Total number of adverse events in the elderly and non-elderly patients

	Elderly patients	Non-elderly patients
No. of total patients enrolled	56	141
No. of patients who experienced adverse events	31	79
Percentage of patients who experienced adverse events	55.4	56.0

Table 5 Causes of discontinuation and numbers of patients in whom the study drugs were discontinued due to adverse events in the elderly and non-elderly groups

Elderly patients	Non-elderly patients
16 w Malaise, Anorexia[1]	18 w Elevation of ALT[1]
6 w Malaise, Anorexia[1]	6 w Elevation of ALT[1]
6 w Elevation of ALT[1]	2 w Pyrexia[1]
8 w Elevation of ALT[1]	3 w Pyrexia
3 w Pyrexia	13 w Sepsis due to hemolytic streptococcus[1]
4 w Cough	18 w Abdominal fullness[1]
18 w Development of HCC[1]	2 w Elongation of PT
	3 w Elevation of total bilirubin[1]
	18 w Development of HCC[1]
Total 7/56 (12.5%)	9/141 (6.4%)

[1]Patients achieved sustained virological response at 24-wk. Level of elevation of ALT and total bilirubin at which the drug was discontinued: 200 INU (5-folds of normal) for ALT and 3.0 mg/dL for total bilirubin. HCC: Hepatocellular carcinoma; ALT: Alanine aminotransferase.

the numbers of patients in whom the drugs were discontinued due to adverse effects in each group. The levels of elevation of ALT and total bilirubin at which the drug was discontinued were 200 INU (5-folds of normal) for ALT and 3.0 mg/dL for total bilirubin. In the elderly group, 7 out of 56 cases (12.5%) were discontinued, and in the non-elderly group, 9 out of 141 (6.4%). The ratio of discontinuation was greater for the elderly patients but the difference was not significant (P = 0.336). The ratio of patients who achieved SVR_{24} in the discontinued due to side effects subgroup was 71.4% (5/7) in the elderly and 77.8% (7/9) in the non-elderly patients (Table 2).

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Informed consent was obtained from all patients for being included in the study. The protocol was approved by the ethics committees/institutional review boards of participating centers and conformed to Good Clinical Practice guidelines and Declaration of Helsinki principles. This article does not contain any studies with animal subjects.

DISCUSSION

In recent years, patients presenting with HCV-associated chronic hepatitis or liver cirrhosis have been older, especially those patients with liver cirrhosis[5-7]. Among these patients, the occurrence of HCC is also increasing. It is generally well accepted that aging is a potent risk factor for HCC development in patients with HCV-associated liver disease[7-11]. Peg-IFNα/RBV therapy was shown to be effective in preventing the development of HCC in younger patients[12]; however, older patients are poor candidates for Peg-IFNα/RBV therapy.

More recently, oral dual therapy with daclatasvir/asunaprevir was demonstrated to be very effective in eradicating HCV infection. Overall, 76.7% of patients achieved SVR_{12} and SVR_{24} in an initial trial[2].

In this study, we demonstrated that the proportion of patients with SVR at 24 wk post-treatment was almost the same among elderly patients (≥ 75 years old), who were thought to have longer durations of HCV infection, as among younger patients (< 75 years old, 91.1% *vs* 90.1%).

We also demonstrated that the degree of side effects

was nearly the same in the elderly and younger patients. Hitherto, no report has dealt with age differences in the efficacy and side effects of oral dual administration of daclatasvir/asunaprevir. The question remains: Is there any essential benefit in eradicating HCV in elderly patients (≥ 75 years old) with HCV-associated liver disease by administering daclatasvir/asunaprevir?

There is much evidence that the eradication of HCV virus (*i.e.*, SVR) by IFN or Peg-IFNα/RBV treatment brings about a low incidence of HCC development[12-18]. Yet, there is no definite evidence that the eradication of HCV virus by dual therapy with daclatasvir/asunaprevir can bring about a low incidence of HCC in SVR patients. There is some potential, however, for these drugs to lower the risk of HCC development. First, there is some evidence of lowering serum alfa-fetoprotein (AFP) levels after eradicating HCV virus by the dual therapy, which is one of the potential risk factors for HCC development in HCV-associated liver diseases[19-24]. Oka *et al*[25,26] actually demonstrated that the serum AFP level was a potential risk factor for HCC development in cirrhotic patients.

Karino *et al*[20] compared the changes of serum AFP levels after treatment by Peg-IFNα/RBV and by daclatasvir/asunaprevir treatment; they were 13.7→4.9 ng/mL on average for Peg-IFNα/RBV and 15.2→4.8 ng/mL for daclatasvir/asunaprevir. Moreover, the proportions of patients who showed below 5 ng/mL after SVR were 56% in Peg-IFNα/RBV and 65% in daclatasvir/asunaprevir treatment, suggesting nearly the same effect on AFP levels with both treatments. More recently, Miyaki *et al*[24] examined the changes in AFP levels before and after the dual therapy (median 27 mo after the completion of the therapy), and found a significant decrease in SVR patients (AFP levels decreased to within the normal limit in all patients by 18 mo after treatment).

Second is the potential of dual therapy with daclatasvir/asunaprevir to reduce liver fibrosis. Miyaki *et al*[24] also observed the changes of liver fibrosis markers before and after the administration of the drugs and found a significant increase in platelet counts and a significant decrease in liver fibrosis markers such as hyaluronic acid, type Ⅳ collagen and M2BPGi (a liver fibrosis glycobiomarker) at 27 mo (median) after completion of the treatment. van der Meer *et al*[27] also demonstrated a significant increase in the platelet counts associated with a decrease in spleen volume after the completion of IFN therapy.

There is some evidence that eradication of HCV-virus by IFN might bring about a decrease in the fibrosis staging score of HCV-associated chronic hepatitis. Shiratori *et al*[28] demonstrated that the fibrosis score after IFN therapy had regressed in patients with a sustained response at a rate of -0.28 U/year in the histological examination of the biopsied specimens, suggesting that the staging of fibrosis might be reduced by one step in every 4 years by IFN in SVR patients. And, it is well known that the staging of fibrosis has a close association with the incidence of HCC development[29]. Omata[29] surveyed the relationship between the degree of fibrosis and the incidence of HCC in HCV-associated chronic hepatitis and found that the incidence of HCC was 0.46%/year in patients with slight fibrosis (F1 stage), while in patients with moderate fibrosis (F3 stage) it was 3%/year, and in patients with severe fibrosis (F4 stage) it was 7%/year.

In support of this concept, van der Meer *et al*[27] demonstrated an increase in platelet counts associated with a decrease in spleen volume in the IFN-treated SVR patients among HCV-associated patients with Ishak 4-6 fibrosis, and concluded that the portal hypertension was decreased in those patients.

Considering the above evidence, it is possible that the eradication of HCV virus by dual therapy with daclatasvir/asunaprevir might bring about reduction in fibrosis and a lower incidence of HCC development even in patients over 75 years old, who have an impending risk of HCC development.

However, long-term observations of SVR patients after therapy with daclatasvir/asunaprevir will be necessary to make any final conclusions about the effect on prevention of HCC development.

COMMENTS

Background

Recently, direct acting antivirals (DAAs), including dual therapy with daclatasvir/asunaprevir, have been widely used in the therapy of chronic hepatitis C virus (HCV) genotype Ib infection. Dual therapy with daclatasvir/asunaprevir was demonstrated to be highly effective without serious side-effects. However, those results were studied in the non-elderly (patients under 70 years old). The effectiveness and safety in the elderly patients (> 70 years old) should be studied.

Research frontiers

Although, DAAs were widely used in the treatment of HCV-associated liver diseases, few prior reports surveyed the difference in the efficacy and side effects of dual oral therapy with daclatasvir/asunaprevir between elderly patients and non-elderly patients.

Innovations and breakthroughs

In this study, the effectiveness and safety of the therapy with daclatasvir/asunaprevir were demonstrated in elderly patients as well as in non-elderly patients.

Applications

In Japanese, recently the aged population is increasing rapidly among cases of HCV-associated liver disease, and these individuals are at high risk for developing hepatocellular carcinoma. Eradicating HCV in this population is important and many approaches have been proposed. Now, the authors can eradicate HCV by oral therapy with daclatasvir/asunaprevir effectively and safely.

Peer-review

The manuscript is an interesting one, discussing a very important issue as regarding new DAAs with HCV treatment.

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ORIGINAL ARTICLE

Observational Study

Factors associated with success of telaprevir- and boceprevir-based triple therapy for hepatitis C virus infection

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Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at kian.bichoupan@mssm.edu. Consent was not obtained but the presented data are anonymized and risk of identification is low.

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Abstract

AIM

To evaluate new therapies for hepatitis C virus (HCV), data about real-world outcomes are needed.

METHODS

Outcomes of 223 patients with genotype 1 HCV who started telaprevir- or boceprevir-based triple therapy (May 2011-March 2012) at the Mount Sinai Medical Center were analyzed. Human immunodeficiency virus-positive patients and patients who received a liver transplant were excluded. Factors associated with sustained virological response (SVR24) and relapse were analyzed by univariable and multivariable logistic regression as well as classification and regression trees. Fast virological response (FVR) was defined as undetectable HCV RNA at week-4 (telaprevir) or week-8 (boceprevir).

RESULTS

The median age was 57 years, 18% were black, 44% had advanced fibrosis/cirrhosis (FIB-4 $\geqslant$ 3.25). Only 42% (94/223) of patients achieved SVR24 on an intention-to-treat basis. In a model that included platelets, SVR24 was associated with white race [odds ratio (OR) = 5.92, 95% confidence interval (CI): 2.34-14.96], HCV sub-genotype 1b (OR = 2.81, 95%CI: 1.45-5.44), platelet count (OR = 1.10, per x 10^4 cells/μL, 95%CI: 1.05-1.16), and *IL28B* CC genotype (OR = 3.54, 95%CI: 1.19-10.53). Platelet counts > 135 x 10^3/μL were the strongest predictor of SVR by classification and regression tree. Relapse occurred in 25% (27/104) of patients with an end-of-treatment response and was associated with non-FVR (OR = 4.77, 95%CI: 1.68-13.56), HCV sub-genotype 1a (OR = 5.20; 95%CI: 1.40-18.97), and FIB-4 $\geqslant$ 3.25 (OR = 2.77; 95%CI: 1.07-7.22).

CONCLUSION

The SVR rate was 42% with telaprevir- or boceprevir-based triple therapy in real-world practice. Low platelets and advanced fibrosis were associated with treatment failure and relapse.

Key words: Sustained virologic response; Hepatitis C virus; Relapse; Telaprevir; Boceprevir; Triple-therapy; Classification and regression; Adverse event; Real-world

Core tip: A cohort of 223 hepatitis C virus (HCV)-infected patients at a tertiary referral center was analyzed. All patients were treated with telaprevir and boceprevir. Using both logistic regression and a machine learning techniques we identified baseline and on-treatment factors associated with sustained virologic response and relapse. We found that both low platelet count and advanced fibrosis or cirrhosis were associated with treatment failure. Information of the effectiveness of these protease inhibitors could be used to inform clinical trials of future HCV direct-acting antivirals.

Bichoupan K, Tandon N, Martel-Laferriere V, Patel NM, Sachs D, Ng M, Schonfeld EA, Pappas A, Crismale J, Stivala A, Khaitova V, Gardenier D, Linderman M, Olson W, Perumalswami PV, Schiano TD, Odin JA, Liu LU, Dieterich DT, Branch AD. Factors associated with success of telaprevir- and boceprevir-based triple therapy for hepatitis C virus infection. *World J Hepatol* 2017; 9(11): 551-561 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i11/551.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i11.551

INTRODUCTION

The hepatitis C virus (HCV) infects about 3% of the world's population. In the United States, HCV chronically infects an estimated 2.7 to 3.9 million people and is a leading cause of liver disease, liver cancer, and liver-related death[1,2]. In 2012, the Centers for Disease Control and Prevention announced a public health initiative to identify HCV-positive individuals and transition them into care[1]. The recommendation for increased screening was affirmed by the United States Preventive Services Task Force[3]. The goal of treatment is to induce a sustained virological response (SVR) and thereby interrupt, and potentially reverse the progression of liver disease, improve the quality of life, and reduce the risk of transmission.

In the era of direct-acting antiviral (DAAs) drugs, treatment for HCV is evolving rapidly. Data about outcomes in real-world clinical practice are needed to evaluate new medications. The first generation protease inhibitors, telaprevir (TVR) and boceprevir (BOC), were approved for treatment of genotype 1 HCV in combination with pegylated-interferon (PEG) and ribavirin (RBV) in 2011. In clinical trials, overall SVR rates ranged from 64% to 75% for TVR-based triple therapy and from 59% to 66% for BOC-based triple therapy[4,5]. These trials enrolled relatively few patients $\geqslant$ 65 years of age and few with liver cirrhosis[6-8], although these patients are often in great need of treatment. Triple therapy with TVR or BOC is no longer the standard of care in the

United States and is no longer recommended by the American Association for the Study of Liver Disease and the Infectious Disease Society of America[9]; however, the effectiveness of these regimens in real-world practice may offer important information about currently available NS3/4A protease inhibitors. Information about their real-world effectiveness may benefit providers and patients in these regions of the globe.

Past investigations of factors associated with treatment outcome have yielded varied results[4,10]. Among patients receiving TVR-based therapy, the absence of fibrosis or cirrhosis has been associated with SVR[4,10-12]. Younger age was associated with SVR in one study[4], but not in others[12,13]. Among patients receiving BOC-based triple therapy, younger age and lower fibrosis stage were associated with SVR among treatment-naïve patients, but not among treatment-experienced patients[4,7]. A study of veterans receiving either TVR- or BOC-based triple therapy found that failure to achieve SVR was associated with cirrhosis, prior null or partial response, *IL-28B* CT or TT genotype, high baseline viral load, black race, diabetes, high aspartate transaminase (AST) to platelet ratio index (APRI) and FIB-4 scores, low platelet counts, and low LDL cholesterol[14].

TVR- and BOC-based triple therapies cause side effects and adverse events, including anemia, neutropenia, thrombocytopenia, rash, and liver decompensation[4,13-16], which can lead to dose reductions and treatment discontinuations[4,7,14]. Several deaths have been reported[17]. A key clinical question is which patients should be treated now, and which should be advised to wait for less toxic and more effective therapies. A major concern is that the rate of liver damage may accelerate with age[18]. Modeling studies predict that HCV-related morbidity and mortality will increase sharply in the years ahead[19,20]. The aging of the HCV-positive population and the age-dependent increase in the risk of HCV-related morbidity and mortality create a need to develop and deploy HCV therapies as safely and effectively as possible.

In real-world clinical practice little is known about the factors associated with SVR rates and relapse with DAA's. This project investigates these factors and provides a benchmark for comparing newer therapeutic agents to the first generation protease inhibitors. We were especially interested in factors that may worsen over time, such liver fibrosis stage and platelet counts.

MATERIALS AND METHODS

Study subjects and methods of data collection

The study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the IRB of Mount Sinai (GCO #: 10-0032). The need for informed consent was waived as the work did not alter standard clinical practice. The study group was composed of 223 adults who initiated triple therapy with PEG-IFN/RBV and TVR or BOC (HCV NS3/4A protease inhibitors) at the Mount Sinai Medical Center between May 2011 and March 2012. Providers submitted names of patients and Mount Sinai's electronic database was queried to capture the complete cohort of patients. The electronic database query identified patients with an ICD-9 code for HCV and a prescription for either TVR or BOC. Medical records were reviewed to verify patients identified through electronic phenotyping. All patients included in the analysis received at least one dose of TVR or BOC. Human immunodeficiency virus-positive patients and patients who previously received a liver transplant were excluded.

Data about the HCV treatment regimen, age, gender, race, body mass index (BMI), *IL28B* genotype, baseline clinical laboratory values [albumin, hemoglobin, AST, alanine transaminase (ALT), platelets, creatinine, ferritin, information to calculate the estimated glomerular filtration rate (eGFR), and alpha-fetoprotein (AFP)], indicators of liver fibrosis, past medical history, including diabetes (indicated by at least one of the following-prescription for metformin, pioglitazone, insulin, a recorded diagnosis of diabetes, fasting glucose above 125 mg/dL, or hemoglobin A1c above 6.5%), depression (indicated by use of at least one of the following medications-wellbutrin, aripiprazole, bupropion, citalopram, venlafaxine, escitalopram, paroxetine, or sertraline), outcome of prior HCV treatment, HCV sub-genotype and viral load were extracted from medical records. On-treatment changes in HCV viral load, ferritin, estimated GFR using the Chronic Kidney Disease Epidemiology Collaboration formula[21] were calculated and incident anemia (hemoglobin below 9 g/dL) was recorded.

If available, biopsy or transient elastography data were used to classify liver disease as cirrhosis (yes/no). Cirrhosis was defined as a liver biopsy score of 4 using the Batts-Ludwig system or a transient elastography value > 13.5 kPa. In addition, liver fibrosis stage was estimated from the APRI and the FIB-4 score. APRI scores > 1.5 and FIB-4 scores > 3.25 were coded as advanced fibrosis/cirrhosis. APRI and FIB-4 scores were calculated as follows: APRI = AST (U/L)/(upper limit of normal)/[platelet count (10^9/L) × 100][22-24]; FIB-4 = age (years) × AST (U/L)/[platelet count (10^9/L) × ALT (U/L)$^{1/2}$][25,26]. The FIB-4 score is reliable and has been tested and validated in large HCV mono-infected cohorts[27].

The standard treatment regimens are outlined in supporting Figures 1 (TVR) and 2 (BOC). Patients on TVR received 12 wk of TVR in combination with PEG/RBV. After week 12, TVR was discontinued. PEG/RBV dual therapy was continued for an additional 12 or 36 wk depending on prior treatment response, the presence of cirrhosis, and viral kinetics. With the exceptions noted below, patients on BOC-containing regimens began treatment with 4 wk of PEG-IFN/RBV dual therapy. Then BOC was added and patients received triple therapy for 24 to 44 wk depending on prior treatment response, the presence of cirrhosis and viral kinetics. Eight patients did not receive the standard PEG-IFN/RBV lead-in prior to starting BOC: Six did not have a lead-in phase, one received 19 wk of lead-in, and one received 24 wk of lead-in. Seventy-two patients, 63 on TVR and 9 on BOC, met the eligibility criteria for consideration of response

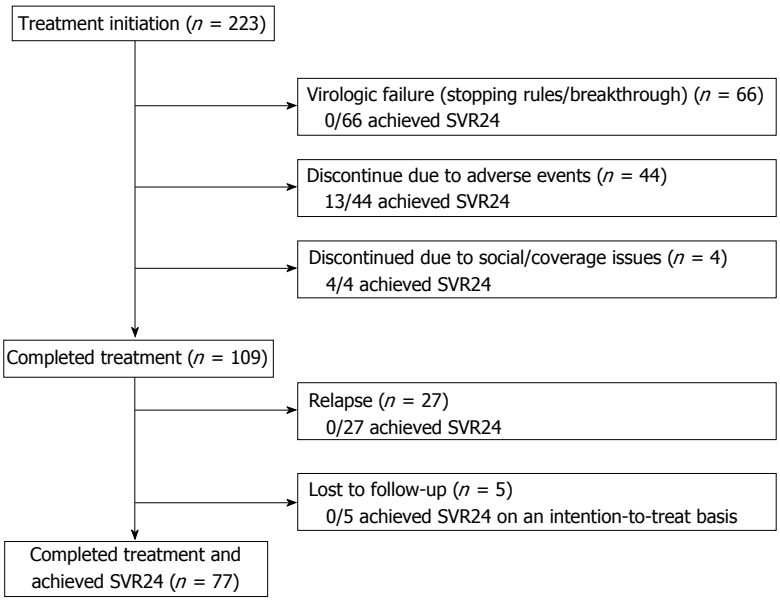

Figure 1 Outcomes of 223 patients inititating telaprevir- or boceprevir-based triple therapy. SVR: Sustained virological response.

guided therapy. Virologic stopping rules were followed.

During treatment, follow-up visits were scheduled for weeks 4, 8, 12, 24, 48, 60 and 72. Anemia was managed at the discretion of the provider. Generally, RBV dose was reduced at hemoglobin levels ⩽ 10 g/dL. If hemoglobin levels remained low, erythropoietin was administered. Blood transfusions were used to treat intractable anemia[9]. Eltrombopag was not used.

SVR was defined as the absence of HCV RNA six months after the end-of-treatment (EOT), as measured by a real-time-polymerase chain reaction assay (Roche Cobas/Ampliprep Cobas Taqman version 2.0, Roche Molecular Systems Inc., Branchburg, NJ, United States). An HCV viral load below the lower limit of detection (18 IU/mL) was recorded as undetectable. Relapse was defined as the detection of HCV RNA after the absence of HCV RNA at EOT. A fast virologic response (FVR) was defined as undetectable HCV RNA 4 wk after the initiation of TVR or 8 wk after the initiation of BOC-based treatment.

Statistical analysis

Subgroups were compared using *t*-tests or Mann-Whitney tests for continuous variables and χ^2 or Fisher-exact tests for categorical variables. Pearson correlation tests were used to assess associations between continuous variables. Univariable and multivariable logistic regression were used to analyze the association between the baseline factors listed above and SVR calculated on an intention-to-treat basis. Models for relapse were built using data from patients who completed the planned treatment regimen, had undetectable HCV RNA at the EOT, and who were not lost to follow-up. Factors with a *P*-value below 0.15 in univariable models were included in multivariable analyses; variables with a *P*-value below 0.05 were retained in final models and were considered to be independently associated with the outcome.

When variables were highly correlated with each other, a series of models was built, each with only one member of the pair. In the case of variables that contained common components (*e.g.,* APRI scores and FIB-4 scores) and variables that represent similar disease characteristics (FIB-4 ⩾ 3.25 and histologically/elastography-defined cirrhosis) only one was entered into a model at a time. Missing data for HCV sub-genotype and *IL28B* polymorphism were imputed as 1a or CT/TT, respectively. A sensitivity analysis was conducted to determine whether variables associated with SVR were specific to one of the two protease inhibitors. Regression analyses were conducted on a dataset containing patients on TVR alone.

Classification and regression trees (CARTs) were built to identify baseline factors associated with SVR. Factors in the tree included race, cirrhosis (FIB-4 score), diabetes, HCV sub-genotype, *IL28B* genotype, history and previous response to HCV treatment (naïve/relapse *vs* null/intolerant), and platelet count.

The significance level was set to 0.05. Statistical analyses were conducted with SPSS and SAS.

RESULTS

Characteristics of the study group and treatment outcomes

Two complementary approaches were used to identify cases and ensure that the entire cohort of patients meeting the entry criteria were included. The traditional approach (patients identified by their providers) yielded 209 patients. A query of the Mount Sinai data warehouse identified an additional 14 patients, yielding a total of 223 patients whose baseline characteristics are presented in Table 1. One hundred and seventy-two (77%) were treated with TVR and 51 (23%) were

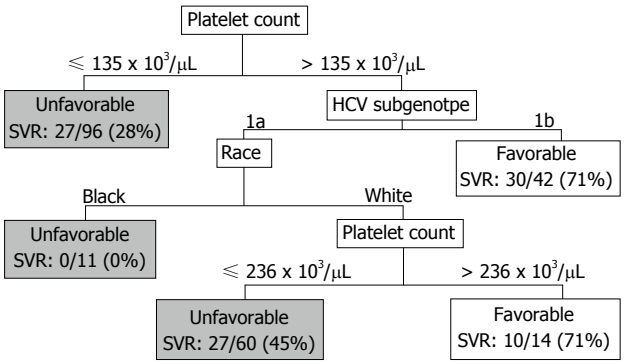

Figure 2 Classification and regression trees analysis of baseline factors associated with sustained virologic response. SVR: Sustained virologic response; HCV: Hepatitis C virus.

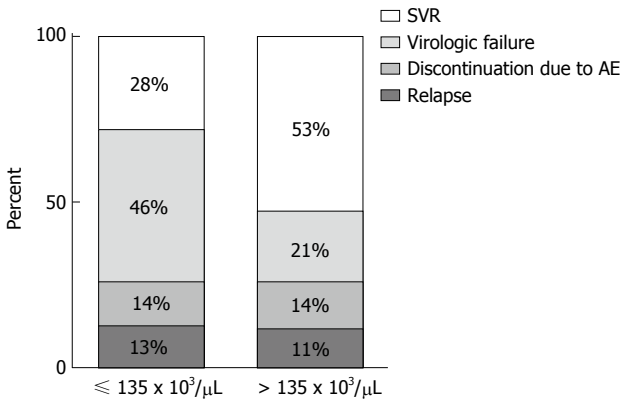

Figure 3 Treatment outcome stratified by low and high baseline platelet count. Treatment outcomes of patients with platelets ⩽ 13.5 × 10^4/μL and > 13.5 × 10^4/μL are shown in a stacked column graph. The SVR rate in the low platelet group was 28% *vs* 53% in the high platelet group. SVR: Sustained virologic response.

treated with BOC. The patients were predominantly male (65%) with a median age of 57 years (range: 22-74) and a BMI of 27.1 kg/m^3 (range: 16.3-49.3). Eighteen percent were black. Liver biopsy and/or transient elastography data were available for 202/223 (91%) patients of whom 96/202 (48%) had cirrhosis.

Figure 1 diagrams treatment outcomes. Of the 223 patients who initiate treatment, 66 patients had virologic failure during treatment; 44 discontinued treatment early due to adverse events (13 achieved SVR); four discontinued due to social/coverage issues (four achieved SVR); 109 (49%) completed the intended treatment regimen and were viral load negative at the EOT, but 27 relapsed and five did not return for testing at week-24 post EOT and could not be reached after repeated attempts by providers to contact them. On an intention-to-treat basis, the overall SVR rate was 42%. The overall SVR rate was 45% (77/172) for patients on TVR and 33% (17/51) for patients on BOC (P = 0.15) in an unadjusted analysis that did not correct for baseline differences. The SVR rates for treatment-naïve, prior non-responders, prior-interferon intolerant patients, and prior relapsers were 41%, 35%, 33% and 62%, respectively (P = 0.04).

Baseline factors associated with SVR

The baseline characteristics of the SVR and non-SVR groups are presented in Supporting Table 1. The SVR group had a significantly higher proportion of patients with the favorable *IL28B* CC genotype, with HCV sub-genotype 1b and higher levels of albumin and platelets, and this group had a significantly lower proportion of blacks, patients with diabetes, liver cirrhosis, a history of non-response to PEG/RBV treatment, lower levels of AFP and AST, and lower APRI and FIB-4 scores. Univariable logistic regression analysis of baseline variables showed *IL28B* CC genotype, higher platelets, higher albumin, HCV sub-genotype 1b, an HCV treatment history that included no prior treatment or relapse were positively associated with SVR and that black race, diabetes, high AST, high AFP, diagnosis of cirrhosis, or and advanced fibrosis/cirrhosis with APRI >1.5 or FIB-4 ⩾ 3.25 were negatively associated with SVR (Table 2).

Before building multivariable models, the Pearson's correlation coefficient for pairs of variables was determined to ensure that two highly correlated variables were not included in the same model. The multivariable logistic regression model shown in Table 2 includes the platelet count and excludes variables highly correlated with the platelet count. SVR was positively associated with *IL28B* CC genotype [odds ratio (OR) = 3.54, 95% confidence interval (CI): 1.19-10.53], higher platelet counts (OR = 1.10, per x 10^4 cells/μL, 95%CI: 1.05-1.16), white race (OR = 5.92, 95%CI: 2.34-14.96) and sub-genotype 1b HCV (OR = 2.81, 95%CI: 1.45-5.44). Four additional logistic regression models were built in which the platelet count was excluded and variables that are highly correlated with platelet count were examined individually (Table 2). In all four models white race, sub-genotype 1b, and CC *IL28B* genotype were positively associated with SVR. Variables indicative of more advanced liver disease - lower albumin, higher FIB-4 score, cirrhosis on biopsy/fibroscan - were significantly associated with treatment failure in individual models. A forest plot showing the interaction between treatment history and various baseline characteristics on outcome is presented in Supporting Figure 3.

An additional multivariable logistic regression analysis was conducted on the subgroup of patients receiving TVR-based triple therapy. Results were similar to those for the entire study group. SVR was positively associated with platelets (OR = 1.07 per × 10^4 cells/μL; 95%CI: 1.01-1.14), white race (OR = 5.22; 95%CI: 1.76-15.50), and HCV sub-genotype 1b (OR = 3.27; 95%CI: 1.51-7.07).

On-treatment factors associated with SVR

Table 3 shows the association between SVR and changes that occurred during treatment. As expected, SVR was strongly associated with viral kinetics. Patients whose HCV viral load decreased rapidly after starting the protease inhibitor and who thus had a FVR were significantly more likely to achieve an SVR (P < 0.01). SVR was also significantly associated with a greater decrease in

Table 1 Baseline characteristics of the study group

	n	Continuous variables: Median (IQR)/categorical variables: *n* (%)	Range
Telaprevir	223	172 (77)	-
Demographics and anthropometrics			
Age, yr	223	57 (51-61)	22-74
Gender, male	223	144 (65)	-
Race, white	223	182 (82)	-
BMI, kg/m^3, 17-24: Normal; 25-30: Overweight; > 30: Obese[a]	186	27.1 (24.5-30.7)	16.3-49.3
Past medical history			
Diabetes	223	48 (22)	-
Depression	223	47 (21)	-
IL28B genotype	223		
CC		20 (9)	-
CT		50 (22)	-
TT		21 (10)	-
Unknown		132 (59)	-
Treatment history	223		
Naïve		68 (31)	-
Non-responder		95 (43)	-
Relapser		45 (20)	-
Intolerance		12 (5)	-
Unknown		3 (1)	-
HCV treatment related characteristics			
HCV viral load, log IU/mL	221	6.31 (5.89-6.66)	3.07-7.64
Sub-genotype	223		
1a		118 (53.5)	-
1b		72 (32)	-
1a/1b		1 (0.5)	-
Unknown		32 (14)	-
Laboratory tests			
Hemoglobin, g/dL, female:12-15.5 g/dL; male: 13.5-17.5 g/dL[a]	220	14.3 (13.2-15.3)	9.2-18.2
AFP, ng/mL, 1.6-4.5 ng/mL[a]	158	6.85 (3.58-13.83)	0.80-208.60
Albumin g/dL, 3.5-4.9 g/dL[a]	219	4.20 (3.90-4.50)	2.60-5.30
AST, U/L, 1-50 U/L[a]	221	62 (39-106)	19-324
ALT, U/L, 1-53 U/L[a]	221	67 (44-107)	15-403
Platelets, × 10^3/μL, 150-450 × 10^3/μL[a]	223	152 (106-195)	14-365
Creatinine, mg/dL, 0.60-1.40 mg/dL[a]	205	0.91 (0.81-1.04)	0.58-10.2
Ferritin, ng/mL, 15-150 ng/mL[a]	54	184 (113-373)	22-893
eGFR, mL/min/1.73 m^2 < 60 mL/min per 1.73 m^2[ab]	204	88 (75-99)	6-125
Indication of liver fibrosis			
APRI score	221	0.82 (0.43-1.82)	0.10-12.48
FIB-4 score	221	2.65 (1.77-5.66)	0.35-35.30
FIB-4, advanced fibrosis/cirrhosis[c]	221	98/221 (44)	-
Cirrhosis, biopsy	189	85/189 (45)	-
Transient elastography score, kPa	80	11.8 (7.2-20.3)	3.9-55.1
Cirrhosis, transient elastography[d]	80	36/80 (45)	-
Cirrhosis, transient elastography/biopsy	202	96/202 (48)	-

[a]Normal range; [b]Estimated glomerular filtration rate calculated with epidemiology formula; [c]FIB-4 score ⩾ 3.25 kPa; [d]Transient elastography > 13.5 kPa. BMI: Body mass index; HCV: Hepatitis C virus; AFP: Alpha-fetoprotein; AST: Aspartate transaminase; ALT: Alanine transaminase; eGFR: Estimated glomerular filtration rate; APRI: Aspartate transaminase to platelet ratio index.

eGFR in the first 4 wk. Treatment discontinuation due to adverse events was less common in the group that achieved SVR than the group that failed therapy (14% *vs* 24%), however, this difference was not statistically significant, $P = 0.06$. There was a trend of patients achieving SVR to having higher median changes in ferritin levels than patients who failed to achieve SVR (146 ng/mL *vs* 62 ng/mL, $P = 0.08$).

Baseline and on-treatment factors associated with relapse

Overall, 109 patients had an undetectable HCV viral load at the time when they completed the intended therapy. Five were lost to follow-up. Relapse was confirmed in 27/104 (25%) of the patients who had follow-up data. Among the patients who were viral load negative at the time treatment ended and who later became viral load positive, the median time to confirmed relapse was 12 wk after the EOT (IQR = 5-12 wk, range = 2-34 wk); however, in some cases, relapse may have occurred before the time it was detected because of missed visits. Multivariable logistic regression analysis revealed an association between relapse and HCV sub-genotype 1a (OR = 5.15; 95%CI: 1.40-18.97) and advanced

Table 2 Univariable and multivariable logistic regression for baseline factors associated with sustained virological response

	Univariable			Multivariable[a]		
	OR	95%CI	*P*	OR	95%CI	*P*
Protease inhibitor, telaprevir	1.62	0.84-3.12	0.15	-	-	-
Age, yr	0.98	0.96-1.01	0.23	-	-	-
Gender, male	1.11	0.64-1.94	0.71	-	-	-
Race, white	3.12	1.41-6.90	< 0.01	5.92	2.34-14.96	< 0.01
Diabetes	0.43	0.21-0.87	0.02	-	-	-
Depression	1.58	0.83-3.02	0.17	-	-	-
BMI, kg/m^2	0.98	0.93-1.04	0.52	-	-	-
IL28B, CC *vs* CT/TT	3.56	1.31-9.64	0.01	3.54	1.19-10.53	0.02
Treatment history, naïve/relapser	1.86	1.08-3.20	0.03	-	-	-
HCV viral load, log IU/mL	0.79	0.54-1.14	0.21	-	-	-
Sub-genotype, 1b (*vs* all other)	2.06	1.17-3.65	0.01	2.81	1.45-5.44	0.02
Hemoglobin, g/dL	1.03	0.86-1.23	0.78	-	-	-
AFP, ng/mL	0.95	0.92-0.98	< 0.01	-	-	-
Albumin, g/dL	2.56	1.33-4.92	< 0.01	-	-	-
AST, U/L	0.99	0.99-0.99	0.02	-	-	-
ALT, per U/L	1.00	0.99-1.01	0.61	-	-	-
Platelets, per × 10^4/μL	1.08	1.03-1.13	< 0.01	1.10	1.05-1.16	< 0.01
Creatinine, per mg/dL	0.8	0.42-1.53	0.50	-	-	-
Ferritin, per ng/mL	0.99	0.99-1.00	0.63	-	-	-
eGFR, per mL/min per 1.73 m^2	1.00	0.99-1.02	0.65	-	-	-
APRI	0.84	0.70-1.02	0.08	-	-	-
FIB-4	0.91	0.83-0.99	0.02	-	-	-
APRI > 1.5	0.44	0.24-0.82	0.01	-	-	-
FIB-4 ⩾ 3.25	0.39	0.22-0.68	< 0.01	-	-	-
Cirrhosis transient elastography/biopsy	0.5	0.29-0.87	0.01	-	-	-

[a]Model includes platelets and no variable significantly correlated with platelets. BMI: Body mass index; HCV: Hepatitis C virus; AFP: Alpha-fetoprotein; AST: Aspartate transaminase; ALT: Alanine transaminase; eGFR: Estimated glomerular filtration rate; APRI: Aspartate transaminase to platelet ratio index.

Table 3 Comparison of on-treatment variables in the sustained virologic response and non- sustained virologic response group

	Total cohort Categorical: *n* (%) Continous: Median (IQR)	SVR (*n* = 94)	Fail to achieve SVR (*n* = 129)	*P*
Discontinuation due to adverse events	44/223 (20%)	13/94 (14%)	31/94 (24%)	0.06[a]
Change in ferritin from baseline to week 4 of treatment, ng/mL	91 (45-212)	146 (81-331)	62 (-20-175)	0.08[b]
Development of severe anemia	94/223 (42%)	54/94 (57%)	66/129 (51%)	0.35[a]
Change in eGFR from baseline to week 4[c], mL/min per 1.73 m^2	-4.41 (-14.87-3.23)	-6.59 (-16.98-0.52)	-1.68 (-13.99-5.00)	0.04[b]
Fast viral kinetics	139/223 (62%)	83/94 (88%)	56/129 (43%)	< 0.01[a]

[a]χ^2 test; [b]Mann-Whitney test; [c]Estimated glomerular filtration rate calculated with epidemiology formula. SVR: Sustained virological response; eGFR: Estimated glomerular filtration rate.

fibrosis/cirrhosis (FIB-4 score ⩾ 3.25; OR = 2.77; 1.07-7.22) (Table 4). The absence of an FVR (OR = 4.77, 95%CI: 1.68-13.56) was the only on-treatment variable independently associated with relapse.

Classification and regression tree analysis of factors associated with SVR

A CART analysis underscored the predictive value of the platelet count and was largely consistent with the results of the logistic regression analysis (Figure 2). The strongest baseline predictor was a platelet count > 135 × 10^3 cells/μL. Among patients with platelets > 135 × 10^3 cells/μL, HCV sub-genotype 1b and white race were predictive of SVR. Among patients with platelets > 135 × 10^3 cells/μL and sub-genotype 1a HCV, platelet counts > 236 × 10^3/μL were predictive of SVR among whites; however, all of the black patients in this subgroup failed therapy. As illustrated in Figure 3, among patients with platelets > 135 × 10^3/μL the virologic failure rate was 21% *vs* 46% in the lower platelet group (P < 0.01), and the SVR rate was 53% *vs* 28% (P < 0.01).

DISCUSSION

This study analyzed treatment outcomes in a real-world cohort of patients treated with TVR- and BOC-based triple therapy by experienced hepatologists. The results are important because TVR-based triple therapy is still used in many parts of the world[28]. Our cohort closely resembles the population of HCV-infected individuals in the United States. Twenty-two percent of the United States population is black, 38% have advanced fibrosis/cirrhosis, and the average age is approximately 50 years with 5% above the age of 65 years[28-31]. In our cohort,

Table 4 Univariable and multivariable logistic regression of factors associated with relapse

	Univariable			Multivariable		
	OR	95%CI	*P*	OR	95%CI	*P*
Protease inhibitor, Telaprevir	0.41	0.15-1.10	0.08	-	-	-
Age, yr	1.00	0.96-1.05	0.95	-	-	-
Gender, female	1.36	0.53-3.48	0.52	-	-	-
Race, black	1.16	0.28-4.71	0.84	-	-	-
Diabetes	1.86	0.65-5.28	0.25	-	-	-
Depression	0.54	0.17-1.75	0.30	-	-	-
BMI, per kg/m^2	0.98	0.88-1.10	0.76	-	-	-
IL28B, CC *vs* CT/TT[a]	-	-	-	-	-	-
Treatment history, naïve/relapser	1.10	0.45-2.72	0.84	-	-	-
HCV viral load, log IU/mL	1.74	0.80-3.78	0.16	-	-	-
Sub-genotype, 1a (*vs* all other)	6.26	1.75-22.45	0.01	5.15	1.40-18.97	0.01
Hemoglobin, g/dL	1.24	0.88-1.73	0.22	-	-	-
AFP, ng/mL	1.02	0.99-1.05	0.15	-	-	-
Albumin, g/dL	1.02	0.34-3.08	0.97	-	-	-
AST, U/L	1.01	1.00-1.02	0.06	-	-	-
ALT, U/L	1.00	0.99-1.01	0.23	-	-	-
Platelets, × 10^4/μL	0.95	0.89-1.02	0.19	-	-	-
Creatinine, mg/dL	1.41	0.72-2.74	0.31	-	-	-
Ferritin, ng/mL	1.00	0.99-1.01	0.26	-	-	-
eGFR, mL/min per 1.73 m^2[b]	0.99	0.97-1.02	0.66	-	-	-
APRI score	1.16	0.94-1.43	0.17	-	-	-
FIB-4 score	1.03	0.94-1.13	0.49	-	-	-
APRI > 1.5	2.33	0.87-6.23	0.09	-	-	-
FiB-4 ⩾ 3.25	2.77	1.12-6.86	0.03	2.77	1.07-7.22	0.04
Cirrhosis, transient elastography/biopsy	2.55	1.05-6.19	0.04	-	-	-

[a]Zero patients with *IL28b* CC genotype relapsed after completing treatment; [b]Estimated glomerular filtration rate calculated with epidemiology formula. BMI: Body mass index; HCV: Hepatitis C virus; AFP: Alpha-fetoprotein; AST: Aspartate transaminase; ALT: Alanine transaminase; eGFR: Estimated glomerular filtration rate; APRI: Aspartate transaminase to platelet ratio index.

18% were black, approximately half had cirrhosis, and 10% were above the age of 65 years. Our most significant findings were the low 42% SVR rate and the association between treatment failure and factors indicative of more advanced liver disease such as low platelets, cirrhosis, high FIB-4 score, high AFP, and low albumin. CART analysis identified platelet counts > 135 × 10^3/μL as the strongest baseline predictor of SVR. Seventy-two percent of patients with platelet counts < 135 × 10^3/μL failed therapy.

Our clinical outcomes are consistent with those of the multicenter CUPIC trial, which examined TVR and BOC in 511 patients with compensated cirrhosis[32]. In both studies, non-responders to dual therapy had low SVR rates, whereas prior relapsers had an SVR rate of 62% in our study and 74% in the CUPIC cohort, supporting the use of triple therapy in prior relapsers. Discontinuations due to adverse events and virologic failure were common in both studies. Only 49% of our cohort and 52% of the CUPIC study group completed the planned treatment. The SVR rate in CUPIC was 48%, similar to the 42% in our study (P = 0.15). These results highlight the need for more effective therapies.

The association we observed between high platelets and SVR is consistent with published data. The relationship between thrombocytopenia and failure to achieve SVR was demonstrated in ENABLE-1 and ENABLE-2[33], two phase Ⅲ multicenter randomized controlled trials in which patients on PEG/RBV were either treated with eltrombopag (a drug that stimulates platelet production) or placebo. In both trials, the SVR rate was significantly higher in the patients receiving eltrombopag: ENABLE-1 (23% *vs* 14%, P < 0.01) and ENABLE-2 (19% *vs* 13%, P = 0.02).

We did not find an association between younger age and SVR. This association was previously reported in a study by Frei and colleagues in which patients < 60 years of age or ⩾ 60 years of age were matched on gender, cirrhosis, HCV genotype, and prior treatment response[34]. Further studies are needed to clarify the relationship between age and SVR among patients receiving triple therapy.

In our study, relapse occurred in about one-quarter of the patients who completed treatment and had an EOT. Relapse is emerging as the most common cause of non-SVR with newer DAAs. Sofosbuvir is an NS5B inhibitor that recently received FDA approval. In clinical trials, 9% of patients treated with sofosbuvir and PEG/RBV relapsed and 22% of patients treated with sofosbuvir and RBV relapsed[35,36]. Simeprevir is an NS3/4A protease inhibitor that recently received FDA approval. In clinical trials of simeprevir, relapse occurred in 11% of treatment-naïve and 18.5% of treatment-experienced patients[37]. In our study, relapse was related to both viral and host factors. HCV sub-genotype 1a and advanced fibrosis/cirrhosis (FIB-4 ⩾ 3.25) were independently associated with relapse. Additionally, the absence of FVR was also associated with relapse, consistent with

results of dual therapy[37]. Recent data suggest that viral double-stranded RNA may play a role in relapse[38]. Understanding the molecular basis of relapse may allow the development of drugs that specifically target the processes underlying this type of treatment failure.

The strengths of our study include the complementary methods used to ensure that the entire cohort of patients was included, use of a study group with a high percentage of blacks, older patients and patients with advanced liver disease who were treated in real-world clinical practice, and use of two methods - multivariable logistic regression and CART analysis - to identify factors associated with treatment outcome. The limitations include the relatively small number of patients on BOC, and the observational study design, which limits the ability to compare the two protease inhibitors to each other.

Unless and until treatments are available that greatly reduce the risk of hepatocellular carcinoma in patients who have advanced liver disease, it will be essential to treat patients before extensive liver damage has occurred, as noted by others[36]. Several newly approved DAAs are available for HCV-infected patients including: Simeprevir, sofosbuvir, and the combination of ombitasvir, paritaprevir with ritonavir, and dasabuvir. In clinical trials, these compounds achieved high SVR rates; however, their effectiveness in the real-world is unknown and needs to be determined. This study provides a standard against which new therapies can be objectively evaluated.

COMMENTS

Background

Hepatitis C virus (HCV) infects 3% of the world's population. In the United States, HCV chronically infects an estimated 2.7 to 3.9 million people and is a leading cause of liver disease. Prior to 2011, treatments for HCV involved pegylated-interferon and ribavirin and had low rates of success. New drugs for HCV-infection, called direct-acting antivirals (DAAs), were first approved in 2011 and provided higher rates of success with lower adverse event rates. Understanding the effectiveness of these DAAs bears relevance for future clinical trials and simulation studies. This paper successfully analyzed a real-world cohort of patients treated with telaprevir- and boceprevir-based therapies to provide better information on cohorts using this class of therapies in the future.

Research frontiers

NS3/4A protease inhibitors are a relatively new class of therapies available to treat HCV-infection. This paper investigates the effectiveness of the first two FDA-approved protease inhibitors for HCV. Understanding the characteristics associated with successful treatment in HCV-infected patients is critical for the ongoing treatment of the HCV-infected population.

Innovations and breakthroughs

The authors used traditional and machine learning methods to identify factors associated with achieving a sustained virologic response in HCV-treatment. The authors found that factors indicative of more advanced fibrosis or cirrhosis were associated with lower rates of sustained virological response. They also found that specific cut-off points in platelet count that could be used to risk-stratify patients. The results imply that treating patients before they develop more advanced disease is an important message that should be relayed to care-providers.

Applications

The results could help improve design of future clinical trials for NS3/4A protease inhibitors for HCV. The population contained individuals with characteristics that were lacking in clinical trials, offering unique information on the effectiveness of NS3/4A protease inhibitors in this population. Currently, numerous protease inhibitors are on the market for HCV. Understanding the risk profile of this class of therapies and the factors associated with their risks and benefits could lead to improvements. Additionally, this real-world study could provide some additional information for future simulation studies to use.

Terminology

Sustained virologic response - the absence of HCV RNA 12-24 wk after the end-of-treatment. Considered a cure in HCV-treatment. Direct-acting antivirals (DAAs) - a class of therapies that directly target HCV and prevent replication. DAAs are composed of NS3/4A protease inhibitors, nucleos(t)ide and non-nucleos(t)ide NS5B Polymerase Inhibitors, and NS5A inhibitors.

Peer-review

This study will give some useful information to clinicians and provided a successful ways to evaluate the new medications. The manuscript read and organized well, and the data treated were also reasonable.

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CASE REPORT

18-Fluoro-deoxyglucose uptake in inflammatory hepatic adenoma: A case report

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Author contributions: Liu W collected the data, performed the literature review and wrote the paper; Delwaide J took care of the patient and collected the data; Bletard N and Delvenne P performed the pathology analyses and figures; Meunier P performed the radiologic investigations; Hustinx R performed the PET-CTs and wrote the manuscript; Detry O followed and operated the patients on and wrote the manuscript.

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Abstract

Positron emission tomography computed tomography (PET-CT) using 18-Fluoro-deoxyglucose (^{18}FDG) is an imaging modality that reflects cellular glucose metabolism. Most cancers show an uptake of ^{18}FDG and benign tumors do not usually behave in such a way. The authors report herein the case of a 38-year-old female patient with a past medical history of cervical intraepithelial neoplasia and pheochromocytoma, in whom a liver lesion had been detected with PET-CT. The tumor was laparoscopically resected and the diagnosis of inflammatory hepatic adenoma was confirmed. This is the first description of an inflammatory hepatic adenoma with an ^{18}FDG up-take.

Key words: Liver surgery; Liver tumor; Liver cancer; Benign tumor; Laparoscopy; Prognosis

Core tip: In cancer therapy, the use of 18-Fluoro-deoxyglucose (^{18}FDG) positron emission tomography computed tomography as a staging or prognostic tool, is increasing. This is also the case for primary or secondary

liver cancer. In this paper, the authors report the first description of an inflammatory hepatic adenoma with ^{18}FDG uptake.

Liu W, Delwaide J, Bletard N, Delvenne P, Meunier P, Hustinx R, Detry O. 18-Fluoro-deoxyglucose uptake in inflammatory hepatic adenoma: A case report. *World J Hepatol* 2017; 9(11): 562-566 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i11/562.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i11.562

INTRODUCTION

Hepatocellular adenomas (HCAs) are rare benign hepatic tumors that are more frequent in women and have been associated with oral contraceptive use[1]. The risk of malignant transformation of HCAs is small but non-negligible[2]. The commonest complication of HCAs is bleeding, an occurrence which has been linked to multiple factors such as the size of the adenoma, pregnancy, visualization of lesional arteries, left lateral lobe location and exophytic growth. Due to these risks, recent guidelines have recommended the resection of adenomas that present: A diameter larger than 50 mm, signs of hepatocarcinoma or focal dysplasia, activated β-catenin mutation, high level of serum alfafoetoprotein, hepatocellular adenomas developing in male gender or hepatocellular adenomas developing in a glycogen storage disease[3]. The resection is regularly performed as laparoscopic hepatectomy[4]. Positron emission tomography computed tomography (PET-CT) using 18-Fluoro-deoxyglucose (^{18}FDG) is an imaging modality that is based on an enhancement of glucose consumption, a distinguishing feature of most cancers that is in part related to the over-expression of GLUT-1 glucose transporters and increased hexokinase activity. The use of PET-CT in primary or secondary liver cancer is increasing[5,6]. As HCAs are benign lesions, they are not assumed to be ^{18}FDG-avid, except in some rare cases. To the best of their knowledge, the authors described herein the first report of ^{18}FDG uptake by an inflammatory HCA (I-HCA), and reviewed the literature for other reports of ^{18}FDG uptake in other types of liver adenoma.

CASE REPORT

A 38-year-old female patient had a past medical history of cervical intraepithelial neoplasia treated with cervical conisation, and a pheochromocytoma that was laparoscopically resected in 2011. She was followed up with yearly magnetic resonance imaging (MRI) that demonstrated a segment 1 liver tumor whose size increased of 20 mm in two years. This 50-mm lesion bore the MRI features of HCA, showing a heterogeneous signal intensity on T-2 weighted images and low-signal intensity on T-1 weighted images. The lesion was slowly and gradually enhanced after injection of gadolinium without significant wash-out on portal phase (Figure 1). In addition, a left renal cyst was noticed, described as type 3 according to the Bosniak classification. An ^{18}FDG PET-CT (Figure 2) was performed to further confirm the nature of the hepatic lesion and exclude extrahepatic metastases. The liver lesion appeared hypermetabolic with a standardized uptake value (SUVmax) of 9.3. A percutaneous biopsy was performed and immunohistology allowed the diagnosis of I-HCA. Blood carcinoembryonic antigen, carbohydrate antigen 19.9 and alphafoetoprotein were negative. A discussion in a multi-disciplinary oncological team meeting led to the decision of the resection of the hepatic lesion. A laparoscopic resection of hepatic segment 1 was performed, extended to segments 2 and 3 due to the location of the tumor at the junction between the inferior vena cava, the left and middle hepatic veins and the left branch of the portal vein. During the same anesthesia, the left kidney mass was resected through a lombotomy, following the preferences of the urologist. The surgical specimen was analyzed and showed slightly clarified hepatocytes scattered throughout the lesion, fibrous tracts with vascular structures within, probably arteries with thick walls (Figure 3). Some inflammatory components surrounded these arteries and there was no significant sinusoidal dilatation. At immunohistochemistry, serum amyloid A was negative and anti-C reactive protein antibodies showed a significant expression of the inflammatory protein around blood vessels, confirming I-HCA (Figure 4). Inflammatory cells were CD3 positive (Figure 5). The immediate post-operative state was excellent, without significant pain and fast oral feeding. The length of hospital stay was 5 d. The patient was seen again one month later for an evaluation visit and no particular problems were observed.

DISCUSSION

This report describes the occurrence of a 50-mm I-HCA that was highly avid for ^{18}FDG at PET-CT. The exact nature of this I-HCA was confirmed by surgical resection. To the best of the authors' knowledge, this is the first report of ^{18}FDG uptake by an I-HCA. HCAs are classified into four types, according to their genetic and histologic features (Table 1): HNF1α inactivated HCA (H-HCA), β-catenin mutated HCA (β-HCA), I-HCA and unclassified HCA[7,8]. The actual risk of malignancy of all HCAs is evaluated at 4.2%[2,3]. The β-HCA subtype is associated with the highest risk of malignant transformation and must be resected (Table 1). After literature review, the authors found 22 other HCA cases with ^{18}FDG uptake in PET-CT[9-19] (Table 2), and none of them was the inflammatory type. Eighteen of them have a description of the histological findings with steatosis. Twelve reported a final diagnosis, which was either HNF1α or hepatic adenomatosis.

The uptake of ^{18}FDG results from the increased metabolism of the cell. The intracellular FDG accumulation is proportional to the amount of glucose utilization[20] and most cancers do have increased cellular activity.

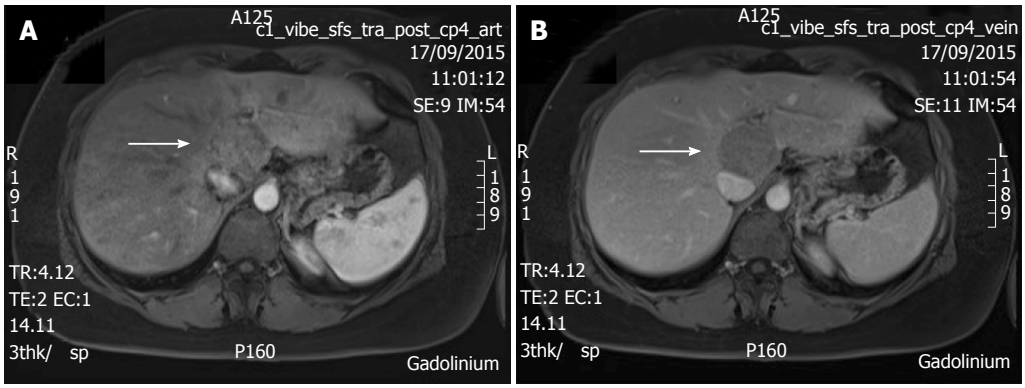

Figure 1 T1 weighted magnetic resonance imaging with gadolinium injection, showing a 50-mm tumor in segment 1 (arrow). A: Arterial phase; B: Portal venous phase.

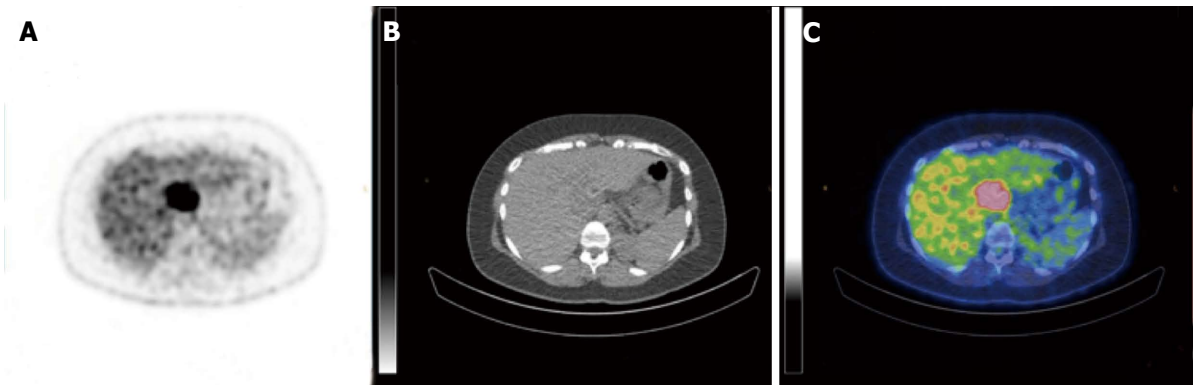

Figure 2 Positron emission tomography computed tomography using 18-fluoro-deoxyglucose showing the 18-fluoro-deoxyglucose avidity of the segment 1 tumor. A: PET; B: CT; C: PET-CT fusion. PET: Positron emission tomography; ^{18}FDG: 18-fluoro-deoxyglucose; CT: Computed tomography.

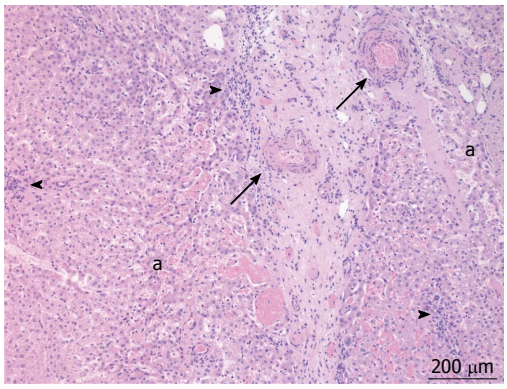

Figure 3 Pathology of the tumor that contains thickened arteries (arrows), inflammatory infiltrate (arrowheads), sinusoidal dilatation (a) (hematoxylin-eosin stain).

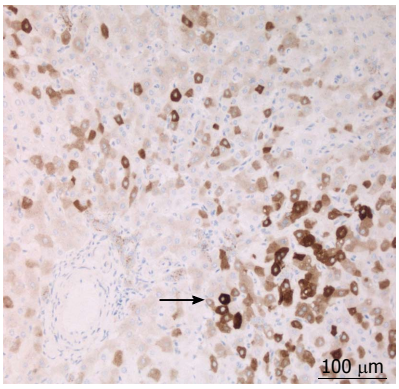

Figure 4 Immunohistochemistry with anti-C reactive protein antibodies, positive in the adenomatous hepatocytes (arrow), confirming inflammatory hepatocellular adenoma.

The differential diagnosis of benign ^{18}FDG avid hepatic lesions might include focal steatosis, infectious, parasitic or inflammatory processes (*e.g.,* hepatic abscess, cryptococcal infection, hepatic tuberculoma) and hepatic adenoma[21,22]. Focal fatty infiltration has been reported to be PET-avid[23]. In fact, as a response to fat accumulation, a subacute inflammatory hepatic reaction with infiltration of activated Kupffer cells may occur, resulting in a higher SUVmax than adjacent normal liver parenchyma. As said above, five cases of hepatic adenoma showed fatty changes but none of them were of the inflammatory type. Only one had a few inflammatory infiltrates. Maybe the fatty change itself was sufficient enough to induce a PET-avid response, without obvious inflammatory infiltrate in histological examination. It is also possible, as suggested by Nakashima *et al*[14], that the high expression of glucose transporters might be responsible for the increased uptake. Indeed, one study demonstrated that in H-HCA the

Table 1 Classification of hepatocellular adenomas

HCA subtype	Abbreviation	Proportion	Markers	Malignant transformation
HNF1α inactivated	H-HCA	35%-40%	LFABP	Rare
β-catenin activated	β-HCA	10%	β-catenin$^+$/GS$^+$ activated	Yes
Inflammatory	I-HCA	50%	CRP$^+$	No
Unclassified	U-HCA	5%	None	No

HCA: Hepatocellular adenoma.

Table 2 Cases of 18-fluoro-deoxyglucose-avid hepatocellular adenomas reported in literature

Ref.	Gender	Age (yr)	Size (mm)	SUVmax	Diagnosis
[7]	Female	41	10	NA	HCA
[8]	Female	37	33	5	H-HCA
[9]	NA	44	30	6.2	HCA
[10]	Female	52	NA	4.09-9.8	Hepatic adenomatosis
[11]	Female	65	30	NA	Necrotic HCA
[12]	Male	69	40	10.4	H-HCA
[13]	4 cases	NA	73 ± 15	6 ± 0.5	HCA
[14]	Female	34	20-30	3.9	HCA
[15]	Male	73	25	11.9	Fatty liver
[16]	Female	44	23	7.9	H-HCA
[17]	9 cases	49 ± 16	27 ± 15	8.2 ± 4.3	H-HCA
This case	Female	38	50	9.3	I-HCA

HCA: Hepatocellular adenoma; ^{18}FDG: 18-fluoro-deoxyglucose; H-HCA: HNF1α inactivated HCA; I-HCA: Inflammatory HCA; NA: Not available.

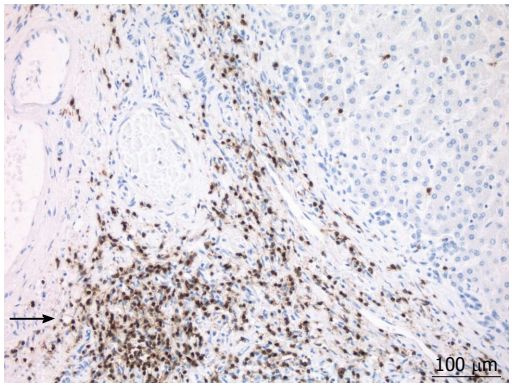

Figure 5 Immunohistochemistry with anti-CD3 antibodies, positive in the inflammatory cells (arrow).

LFABP gene ablation significantly increased the *in-vitro* expression of GLUT-2 but not that of GLUT-1[24]. Another study demonstrated that HNF1α-inactivated HCAs activate glycolysis due to a strong up-regulation of glucokinase[25]. These two components are features of most cancers (rise of GLUT-1 and hexokinase activity) with features of H-HCA (rise of GLUT-2 and glucokinase). However, due to the few reports published in literature, no conclusion can be made on the risk of cancer development in HCA with uptake of ^{18}FDG. Prospective and large series are needed to confirm the role of PET-CT in HCA evaluation and prognosis.

COMMENTS

Case characteristics
A 5-cm liver tumor was diagnosed in a 38-year-old woman.

Clinical diagnosis
This tumor was asymptomatic and described at follow-up imaging after surgical resection of a pheochromocytoma.

Differential diagnosis
Adenoma, hepatocellular carcinoma, other primary or metastatic hepatic tumors.

Laboratory diagnosis
Blood tumor markers, and particularly alphafoetoprotein, were negative.

Imaging diagnosis
Magnetic resonance imaging was compatible with hepatocellular adenoma, but the lesion was 18-fluoro-deoxyglucose (^{18}FDG) avid at positron emission tomography computed tomography (PET-CT).

Pathological diagnosis
Percutaneous biopsy and surgical specimen conformed inflammatory hepatocellular adenoma (I-HCA).

Treatment
Laparoscopic liver R0 resection.

Related reports
To the authors' knowledge, this case is the first report of a PET-CT FDG-avid I-HCA.

Term explanation
Hepatocellular adenomas are benign liver lesions whose imaging diagnosis could be uncertain.

Experiences and lessons
PET-CT positivity is not necessary linked to cancerous degeneration in liver adenomas.

Peer-review

This paper reported a case of PET-avid hepatocellular adenomas and reviews related literature to show variety cause of PET-avid HCA.

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