ISSN 1948-5182 (online)

World Journal of *Hepatology*

World J Hepatol 2016 May 18; 8(14): 607-636

Published by Baishideng Publishing Group Inc

World Journal of Hepatology

A peer-reviewed, online, open-access journal of hepatology

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2014-2017

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World Journal of Hepatology

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Three issues per month Volume 8 Number 14 May 18, 2016

NAME OF JOURNAL
World Journal of Hepatology

ISSN
ISSN 1948-5182 (online)

LAUNCH DATE
October 31, 2009

FREQUENCY
36 Issues/Year (8th, 18th, and 28th of each month)

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PUBLICATION DATE
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DOI: 10.4254/wjh.v8.i14.607

World J Hepatol 2016 May 18; 8(14): 607-615
ISSN 1948-5182 (online)

MINIREVIEWS

Liver resection for intermediate hepatocellular carcinoma

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Author contributions: Yi PS drafted the article; Zhang M designed the study; Zhao JT analyzed and interpreted the data; Xu MQ approved the final version to be submitted; Yi PS and Zhang M contributed equally to this work.

Conflict-of-interest statement: No conflict of interests is declared by the authors.

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Received: January 22, 2016
Peer-review started: January 22, 2016
First decision: March 1, 2016
Revised: March 14, 2016
Accepted: April 21, 2016
Article in press: April 22, 2016
Published online: May 18, 2016

Abstract

Hepatocellular carcinoma (HCC) is one of the most common malignant tumors in China. The Barcelona Clinic Liver Cancer (BCLC) staging system is regarded as the gold standard staging system for HCC, classifying HCC as early, intermediate, or advanced. For intermediate HCC, trans-catheter arterial chemoembolization (TACE) is recommended as the optimal strategy by the BCLC guideline. This review investigates whether liver resection is better than TACE for intermediate HCC. Based on published studies, we compare the survival benefits and complications of liver resection and TACE for intermediate HCC. We also compare the survival benefits of liver resection in early and intermediate HCC. We find that liver resection can achieve better or at least comparable survival outcomes compared with TACE for intermediate HCC; however, we do not observe a significant difference between liver resection and TACE in terms of safety and morbidity. We conclude that liver resection may improve the short- and long-term survival of carefully selected intermediate HCC patients, and the procedure may be safely performed in the management of intermediate HCC.

Key words: Trans-catheter arterial chemoembolization; Intermediate hepatocellular carcinoma; Liver resection; Prognostic factor

Core tip: Trans-catheter arterial chemoembolization (TACE) is recommended as the standard treatment of intermediate hepatocellular carcinoma (HCC) by the Barcelona Clinic Liver Cancer guideline, and this review investigates whether liver resection is better than TACE for intermediate HCC. Based on published studies, we compare the survival benefits and complications of liver resection and TACE for intermediate HCC. We also compare the survival benefits of liver resection in early and intermediate HCC. We find that liver resection could achieve better or at least comparable survival outcomes compared with TACE for intermediate HCC; however, we do not observe a significant difference between liver resection and TACE in terms of safety and morbidity.

Yi PS, Zhang M, Zhao JT, Xu MQ. Liver resection for intermediate hepatocellular carcinoma. *World J Hepatol* 2016; 8(14): 607-615 Available from: URL: http://www.wjgnet.com/1948-5182/full/v8/i14/607.htm DOI: http://dx.doi.org/10.4254/wjh.v8.i14.607

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third most common cause of cancer related death in the world[1]. In China, where about 120 million people are positive for hepatitis B surface antigen, HCC accounts for 300000 deaths every year[2]. It is a great challenge for clinicians to cure HCC. In order to provide standardized treatment for HCC, numerous HCC staging systems have been proposed in recent decades, including the tumor-node-metastasis (TNM) system, the Okuda system, the Barcelona Clinic Liver Cancer (BCLC) system, the Cancer of the Liver Italian Program (CLIP), the Vienna classification, the Chinese University Prognostic Index, the Japan Integrated Staging score, and the Tokyo staging system[3]. All of these staging systems rely mainly on three variables: Tumor characteristics, liver function, and general status. The TNM system is one of the oldest; however, the complexity of its variables has limited its application. The most widely adopted systems for staging HCC are the CLIP and the BCLC system (endorsed by European Association for the Study of the Liver and the American Association For the Study of the Liver)[4]. At present, the BCLC system is regarded as the optimal staging system to predict prognosis and guide treatment of HCC[5].

The BCLC system was proposed by Llovet *et al*[6] in 1999, and validated extensively in 2002, 2005, and 2010[7,8]. Based on the BCLC grading system, the corresponding recommended treatment for each stage is stratified. Curative treatment is advocated for early HCC (defined as a single tumor less than 5 cm in diameter, or up to three tumors less than 3 cm in diameter), such as surgery, radiofrequency ablation, and liver transplantation. For intermediate HCC (a single tumor more than 5 cm in diameter; two to three tumors of which at least one is more than 3 cm in diameter; or more than 3 tumors of any diameter), trans-catheter arterial chemoembolization (TACE) is recommended as the standardized treatment[9-11]. A large proportion of patients in China are classified at diagnosis with intermediate or advanced HCC (any tumor with radiologically evident and histologically proven macro-vascular invasion, spread to lymph nodes and/or distant metastases). Therefore, only a minority of Chinese patients are eligible for radical resection or other curative treatments.

Controversy over the optimal treatment for intermediate HCC has emerged in recent years, as some evidence has suggested that due to the heterogeneity of individuals in liver function and tumor size, patients with intermediate HCC may not all derive the same benefit from TACE. TACE cannot induce complete tumor necrosis, especially when large nodules are encountered. As the mortality and morbidity of liver resection are decreasing worldwide, surgery has been considered in some treatment models[12-14]. One study at Fudan University Hospital endorsed surgical resection for intermediate HCC[15].

This review summarizes research on the role of liver resection in the management of intermediate HCC. Through comparison of liver resection and TACE, we seek to determine an optimal treatment for intermediate HCC.

LIVER RESECTION *VS* TACE FOR INTERMEDIATE HCC

The current treatment algorithm recommends TACE as the standard treatment for intermediate HCC based on two randomized controlled trials[16,17]. However, patients with intermediate HCC vary widely in tumor size, tumor volume, overall health, and other factors, and so derive different benefit from TACE. In recent years, many studies have validated the BCLC treatment recommendation[7,18-23]. Liver resection has been widely performed in patients with intermediate HCC, and many investigators have argued that liver resection is as safe as TACE for intermediate HCC and provides better survival outcomes in selected patients[24-31]. Several centers have proposed their own criteria for judging which intermediate HCC patients are most likely to benefit from liver resection; Zhang *et al*[32] proposed that intermediate HCC cases with the following features should be considered for radical resection: Large or very large solitary tumor with swelling outward, clear border or pseudo-capsule, and less than 30% of the liver destroyed or more than 50% of hepatic hypertrophy; or multiple tumors limited to one segment or lobe. The authors also pointed out that confinement of tumors to one segment or lobe is not an absolute indication, considering that surgical outcomes could be affected by multi-center distribution and the relationship between lesions and major vessels.

Wang *et al*[24] reported that the median overall survival of patients with intermediate HCC after liver resection was significantly higher than that after TACE. Additionally, the 1-, 3- and 5-year survival rates in the liver resection group were also significantly higher than those in the TACE group. The study found that liver resection provided the best survival outcomes for patients with early and intermediate HCC. In accordance with these findings, several studies found similar survival benefits of liver resection in the management of intermediate HCC[24-31]. Another group of investigators performed a propensity score study which enrolled patients with intermediate and advanced HCC, and observed survival benefits of liver resection by total analysis and propensity-matched analysis[29]. In addition,

Table 1 Studies related to complications of liver resection and transhepatic arterial chemotherapy and embolization for intermediate hepatocellular carcinoma

Ref.	Patient	Median OS	Survival rate	DFS	Hospital mortality	Complications
Wang *et al*[24]	LR: 243 TACE: 741	LR: 60.4 TACE: 18.2 Sig	1-, 3- and 5-yr LR: 81.5%, 64.4%, 50.5% TACE: 61.9%, 29.1%, 16.4% Sig	NR	NR	NR
Ho *et al*[25]	LR: 122 TACE: 163	LR: 41.8 TACE: 16.8 Sig	1-, 3- and 5-yr LR: 77.4%, 51.9%, 36.6% TACE: 62.6%, 25.2%, 11% Sig	1-, 3- and 5-yr LR: 60.5%, 32.3%, 24.8%	NR	NR
Lin *et al*[26]	LR: 93 TACE: 73	LR: 27.6 TACE: 18.5	1-, 2- and 3-yr LR: 83%, 62%, 49% TACE: 39%, 5%, 2% Sig	NR	LR: 3/78 (3.8%) TACE: 5/93 (5.4%) No sig	NR
Hsu *et al*[27]	LR: 268 TACE: 455	NR	1-, 3- and 5-yr LR: 81%, 68%, 63% TACE: 30%, 43%, 15% Sig	NR	90 d LR: 4/146 (2.7%) TACE: 12/146 (8.2%) Sig	LR *vs* TACE: Acute liver failure (20% *vs* 11%) Sig Biliary tract injury (6.8% *vs* 0%) Sig
Zhong *et al*[28]	LR: 660 TACE: 319	NR	1-, 3- and 5-yr LR: 91%, 67%, 44% TACE: 83%, 35%, 17% Sig	NR	NR	NR
Zhong *et al*[29]	LR: 257 TACE: 135	LR: 42.9 TACE: 21 Sig	1-, 3- and 5-yr LR: 84%, 59%, 37% TACE: 69%, 29%, 14% Sig After propensity score analysis LR: 87%, 62%, 35% TACE: 77%, 44%, 20% Sig	NR	LR *vs* TACE: 3.1% *vs* 3.7% No sig	LR *vs* TACE: 28% *vs* 18.5% Sig
Yin *et al*[31]	LR: 88 TACE: 85	LR: 41 TACE: 14 Sig	1-, 2- and 3-yr LR: 76.1%, 63.5%, 51.5% TACE: 51.8%, 34.8%, 18.1% Sig	NR	LR: 1/88 (1.1%)	NR

NR: Not reported; OS: Overall survival; DFS: Disease-free survival; Sig: Significant difference; LR: Patients with liver resection; TACE: Patients with transcatheter arterial chemoembolization.

they conducted a subgroup analysis to detect whether patients with liver resection had better survival rates than those with TACE, and survival benefits were observed in subgroup analysis by tumor size, tumor number, macrovascular invasion, and portal hypertension. Given that the heterogeneity of survival rates among different study cohorts, the highest and lowest 5-year survival rates were 63% and 37%, respectively. Due to the variation in regions and characteristics of enrolled patients and surveillance techniques in different centers, the survival rate might differ for these two procedures in different populations, and we cannot recommend that liver resection be the preferred treatment for intermediate HCC in all cases. However, we observed a similar linear trend of survival benefits of liver resection in the studies we examined (Table 1).

Several studies examined the complications and mortality rates of each treatment modality. Two groups of investigators observed that the incidence of complications in patients with liver resection was significantly higher than that in patients with TACE[27,29]. Hsu *et al*[27] noted that the liver resection group had a higher incidence of acute liver failure and biliary duct injury than did the TACE group. However, the incidence of fever was lower in the resection group. Studies reached inconsistent findings about the mortality rates associated with each treatment strategy. Hsu *et al*[27] observed a higher mortality rate in the resection group than in the TACE group, which was contradicted by several other studies[26,29]. This could perhaps be explained by the fact that the proportion of patients aged < 65 years differed between the liver resection group and the TACE group, which likely biased the analysis of mortality. As we know, elements associated with the mortality of patients with HCC include liver function, surgical procedures, and age[33,34]. If the demographic characteristics of patients in different groups are not comparable, we cannot perform a reliable analysis of mortality and complications. Studies providing data related to complications of liver resection and TACE are summarized in Table 1.

LIVER RESECTION IN PATIENTS WITH EARLY AND INTERMEDIATE HCC

The corresponding treatment recommendation for early HCC is a curative strategy such as liver resection, liver

transplantation, or radiofrequency ablation. Many multi-center studies with large sample sizes have validated liver resection for early HCC[35-37]. Generally, patients with intermediate HCC are not candidates for radical resection based on the BCLC treatment algorithm. However, in recent decades, the question of whether liver resection is indicated for intermediate HCC has been debated worldwide. Ng *et al*[38] found the 5-year survival rate to be 39% for intermediate HCC treated by liver resection, which was fairly acceptable. They advocated to perform liver resection in patients with intermediate HCC, and they also demonstrated that liver resection in carefully selected intermediate HCC patients could be as safe as in early HCC patients. Recently, numerous studies have demonstrated that liver resection for intermediate HCC can achieve comparable survival outcomes as in early HCC[18,24,39,40]. Nevertheless, a group of investigators reported survival benefits of liver resection for early HCC[41]. This 10-center study found that disease free survival and overall survival after liver resection were significantly higher for early HCC than for intermediate HCC, but the survival outcomes of liver resection for intermediate HCC were still acceptable, with 5-year survival rate estimated at 57%. They classified the patients receiving liver resection into three groups: BCLC A, BCLC B and BCLC C. The demographic characteristics of the BCLC A and BCLC B groups were not comparable, as both tumor number and average tumor size were lower in the BCLC A group, which may have biased the analysis of survival outcomes. Furthermore, surgical procedures differed significantly between these two groups, with a higher proportion of patients with minor resection in the BCLC A group than in the BCLC B group. Despite the survival advantages in the BCLC A group, the BCLC B group also achieved favorable short- and long-term survival outcomes, in accordance with other findings[35,42,43].

Regarding complications and mortality of liver resection for early and intermediate HCC, two groups of investigators did not observe differences in mortality and morbidity between patients with early and intermediate HCC after liver resection[38,44]. Yamashita *et al*[42] reported that the mortality and morbidity of patients with intermediate HCC receiving liver resection were 3.8% and 24.5%, respectively, which were higher than those in other investigations. The very large tumors (> 10 cm in diameter) of patients in the Yamashita *et al*[42] study may explain the higher mortality and morbidity of this study compared with others. Recent studies comparing liver resection in early and intermediate HCC are presented in Table 2.

A high incidence of recurrence affects the survival rate of patients with HCC after liver resection, and recurrence rate has been identified as an independent prognostic factor for long-term survival[45]. Ng *et al*[38] reported a higher incidence of intrahepatic recurrence after liver resection in intermediate HCC, but found no difference in the extra-hepatic recurrence of patients with early and intermediate HCC after liver resection. Torzilli *et al*[44] conducted a prospective cohort study in 2008, which did not find significant differences in either intrahepatic or extra-hepatic recurrence between patients with early and intermediate HCC receiving liver resection. Another study reported that the estimated 1-, 2-, 3- and 5-year recurrence rates of patients with intermediate HCC after liver resection were 44.2%, 54.5%, 60.6% and 68.1%, respectively[43]. Variables that help predict the risk of HCC recurrence are serum albumin level, microscopic vascular invasion, multi-nodularity, and advanced Edmondson stage[46]. Multi-nodularity and serum albumin level were identified as independent factors of recurrence by Chang *et al*[43]. Given that the incidence of HCC recurrence is fairly high, routine surveillance by computed tomography scan or magnetic resonance imaging is strongly recommended for patients with intermediate HCC after resection[47,48].

PROGNOSTIC FACTORS OF SURVIVAL

Benefits of liver resection are tightly associated with numerous variables, such as liver function, tumor size, and tumor number. Investigators have identified several important variables correlated with survival outcomes of patients with intermediate HCC after liver resection (Table 3). Overall survival is one critical endpoint for the prognosis of patients. One group of investigators found that 8 of 16 variables analyzed had a significant prognostic influence on overall survival by univariate analysis, of which, only 5 variables showed significant prognostic influence by multivariate analysis[38], and they determined that patients without any prognostic risk factors had a higher 5-year survival rate than those with one or more prognostic risk factors. Another group of investigators identified serum albumin level, ICG-15R, tumor capsule, portal hypertension, and other measures as risk markers (variables in different studies related to overall survival are presented in Table 3). Many studies have found that tumor number is a key factor in predicting overall survival[41,49-51], and it is a critical variable in different HCC staging systems. Incomplete radical resection and postoperative recurrence are closely associated with tumor number.

The Child-Pugh grade is another prognostic factor for overall survival that has been clarified by several studies[26,35]. To our knowledge, the Child-Pugh grading is the most widely used system for evaluating liver function. Since liver resection, particularly extensive liver resection, can lead to liver failure in patients with insufficient liver volume, preoperative assessment of liver function will undoubtedly improve the intra-operative safety and postoperative survival rate. Specifically, T4 status of HCC stage was reported to be a prognostic factor of overall survival with a hazard ratio of 5.12 by a liver cancer study group in Japan[42]. However, as this variable is based on tumor size, tumor number, and macro-vascular invasion, we do not classify it as an independent variable for overall survival.

Disease-free survival was another key endpoint in

Table 2 Studies comparing liver resection for Barcelona Clinic Liver Cancer A and B

Ref.	Group	Median OS (mo)	Median DFS (mo)	Accumulative DFS	Intrahepatic recurrence	Extra-hepatic recurrence	Survival rate	Mortality	Morbidity
Ng *et al*[38]	BCLC A: 404 BCLC B: 380	A: 83.5 (67.9-99.1) B: 36.9 (28.9-44.8) Sig	A: 77 (66, 87.9) B: 15.6 (10.8-20.4) Sig	A: 80%, 64%, 40% B: 54%, 38%, 26% Sig	A: 139/404 (34.4%) B: 199/380 (52.4%) Sig	A: 95/404 (23.5%) B: 110/380 (29.0%) No sig	1-, 3- and 5- yr A: 88%, 76%, 58% B: 74%, 50%, 39% Sig	A: 11/404 (2.7%) B: 9/380 (2.4%) No sig	93/404 (23.0%) 104/380 (27.4%) No sig
Cho *et al*[39]	BCLC A: 169 BCLC B: 61	NR	NR	1-, 3- and 5- yr A: 71.4%, 51.8%, 44.1% B: 58.3%, 40.0%, 31.7% No sig	NR	NR	1-, 3- and 5- yr A: 87.5%, 69.5%, 59.0% B: 85.0%, 59.3%, 52.9% No sig	A: 1/169 (0.6%) B: 1/61 (1.6%) No sig	NR
Torzilli *et al*[44]	BCLC A: 61 BCLC B: 24	NR	NR	A: 77%, 30% B: 75%, 35% No sig	A: 19/61 (31.14%) B: 6/24 (25%) No sig	A: 2/61 (3.3%) B: 3/24 (12.5%) No sig	1- and 3-yr A: 91.6%, 81% B: 85%, 67% No sig	A: 0 B: 0 No sig	A: 13/61 (21.3%) B: 7/24 (29.2%) No sig
Wang *et al*[24]	BCLC A: 202 BCLC B: 243	A: Can't estimate B: 60.4	A: NR B: NR	A: NR B: NR	A: NR B: NR	A: NR B: NR	A: Cannot be estimated B: 1-, 3- and 5- yr (81.5%, 64.4%, 50.5%)	NR	NR
Wei *et al*[40]	BCLC A: 52 BCLC: 51	NR	NR	1-, 2- and 3-yr A: 77.8%, 61.4%, 48.9% B: 70.2%, 55.8%, 45.4%; No sig	NR	NR	1-, 2- and 3-yr A: 86.5%, 75.0%, 69.2% B: 84.3%, 68.6%, 54.9% No sig	NR	NR
Chang *et al*[43]	BCLC A: NR BCLC B: 318	NR	NR	5 yr B: 28.6%	The 1-, 2-, 3- and 5-yr recurrence rates were 44.2%, 54.5%, 60.6%, and 68.1%, respectively, in BCLC stage B patients		1-, 2-, 3- and 5-yr B: 81.2%, 68.1%, 59.4%, 46.5%	NR	NR
Ma *et al*[49]	BCLC A: 92 BCLC B: 178	A: Cannot be estimated B: 27.9 ± 3.1 (21.8-33.9)	A: Cannot be estimated B: 16.8 ± 1.65 (13.6-20.0)	NR	NR	NR	NR	NR	NR
Torzilli *et al*[41]	BCLC A: 777 BCLC B: 633	NR	NR	1-, 3- and 5-yr A: 77%, 41%, 21% B: 63%, 38%, 27% Sig	NR	NR	1-, 3- and 5-yr A: 9 5%, 80%, 61% B: 88%, 71%, 57% Sig	30 d A: 1.6% *vs* B: 3.1% No sig	Not significant in major complications
Cucchetti *et al*[35]	BCLC A: NR BCLC B: 247	B: 35 (26-42)	NR	NR	NR	NR	1-, 3- and 5-yr B: 77.8%, 48.7% 33.8%	NR	NR
Yamashita *et al*[42]	BCLC A: Cannot be estimated BCLC B: 53	NR	NR	5-yr B: 24%	Recurrence rate B: 32/53 (62%)		5 yr B: 35%	B: 2/53 (3.8%)	B: 13/53 (24.5%)

OS: Overall survival; DFS: Disease-free survival; A: Patients with HCC of BCLC A; B: Patients with HCC of BCLC B; NR: Not reported; HCC: Hepatocellular carcinoma; BCLC: Barcelona Clinic Liver Cancer; Sig: Significant difference.

prognosis analysis of patients with malignant neoplasms. Microvascular invasion and Child-Pugh class B were two independent factors for disease-free survival in patients with single large or huge HCC[39]. It is known that HCC patients with major vascular invasion have a poor survival rate and high incidence of recurrence[52]. Single large or huge HCC is normally located adjacent to biliary ducts or vessels, making vascular invasion more probable. Alpha-fetoprotein level greater than 400 ng/mL is a significant

Table 3 Prognostic risk factors of overall survival and disease-free survival

Ref.	Prognostic factors of overall survival		Prognostic factors of disease-free survival	
	By univariate analysis	By multivariate analysis	By univariate analysis	By multivariate analysis
Ng *et al*[38]	Hepatitis B surface antigen carrier, serum AFP, symptomatic disease, presence of cirrhosis, number of tumor nodule, microvascular tumor invasion, tumor invasion of adjacent organs, histological margin involvement by tumor	Symptomatic disease, presence of cirrhosis, multi-nodular tumor, microvascular tumor invasion, positive histological margin	Serum AFP level, symptomatic disease, presence of cirrhosis, multi-nodular tumor, microvascular tumor invasion, tumor invasion of adjacent organ, positive histological margins, the presence of microsatellite nodules	Symptomatic disease, presence of cirrhosis, multi-nodular tumor, positive histological margins
Torzilli *et al*[44]	Tumor size, tumor grade	Tumor size, tumor grade	NR	NR
Chang *et al*[43]	NR	Serum albumin level, ICG-15R, serum creatinine, multi-nodularity, Edmondson stage, macro-vascular invasion	NR	NR
Ma *et al*[49]	Histopathological grade, tumor capsule, tumor number, cirrhosis, BCLC classification	Tumor capsule, BCLC classification	NR	Tumor capsule, BCLC classification
Torzilli *et al*[41]	Tumor number, tumor size, macro-vascular invasion, presence of cirrhosis, esophageal varices, major resection, BCLC classification, preoperative bilirubin values	NR	NR	NR
Cucchetti *et al*[35]	NR	Tumor number, presence of esophageal varices, Child-Pugh score	NR	NR
Cho *et al*[39]	Child-Pugh class B, AFP level > 400 ng/mL, histologically poor differentiation	Child-Pugh class B	Positivity of hepatitis B surface antigen, Child-Pugh class B, AFP level > 400 ng/mL, microvascular invasion, histologically poor differentiation	Child-Pugh class B, microvascular invasion
Yamashita *et al*[42]	NR	T4 status of HCC stage by liver cancer study group of Japan, thrombus in portal vein	NR	T4 status of HCC stage by liver cancer study group of Japan, intra-operative transfusion
Lin *et al*[26]	NR	Low albumin level, treatment modality (liver resection *vs* TACE)	NR	NR
Hsu *et al*[27]	NR	Serum AFP level, Child-Pugh class B, performance status ⩾ 2, TACE, tumor size, vascular invasion	NR	NR
Zhong *et al*[28]	NR	Serum AFP ⩾ 400 ng/mL, diabetes mellitus, macro-vascular invasion, portal hypertension, TACE treatment	NR	NR
Yin *et al*[31]	Treatment modality, serum AFP level, total tumor size, tumor number, gender	Tumor number, treatment modality, gender	NR	NR

TACE: Transhepatic arterial chemotherapy and embolization; NR: Not reported; HCC: Hepatocellular carcinoma; BCLC: Barcelona Clinic Liver Cancer; AFP: Alpha fetoprotein.

prognostic risk factor for disease-free survival by multivariate analysis. However, previous studies have demonstrated that minor proportions of patients with HCC do not present with up-regulation of alpha-feto-protein, which makes the surveillance of onset and recurrence of HCC challenging[53-55]. Variables in different studies related to overall survival are presented in Table 3.

CONCLUSION

According to the current BCLC treatment guideline, TACE is recommended as the optimal treatment strategy for intermediate HCC. However, the patients with HCC in Asia distribute among BCLC A, BCLC B, and BCLC C, despite advances in surveillance of HCC in recent years, and a large proportion of patients in Asia present as BCLC B or C when diagnosed. According to the recommendations by the BCLC guideline, these patients cannot benefit from surgical resection. Our review investigated whether liver resection is in fact a viable treatment for intermediate HCC patients.

We found that liver resection could achieve better or at least comparable survival outcomes compared with TACE for intermediate HCC. As for the safety and morbidity, controversy remains. Nevertheless, with advances in surgical equipment and perioperative management, we expect that survival benefits for intermediate HCC after liver resection will improve in the future.

In addition, we examined the outcomes of liver resection in patients with BCLC A and BCLC B. With two exceptions, most studies demonstrated that liver resection offers comparable survival benefits in intermediate HCC and early HCC[38,41]. We conclude that liver resection may improve the short- and long-term survival of intermediate HCC when patients are carefully selected and it may be safely performed in the management of intermediate HCC. However, multi-center randomized controlled trials are needed to clarify which patients are most likely to benefit from liver resection. We identified several key prognostic risk factors for overall survival and disease-free survival. We noted that patients without any prognostic risk factors achieved better short- and long-term survival than those with one or more prognostic risk factors, which indicates that careful selection of patients is critical for satisfactory outcomes in intermediate HCC patients undergoing liver resection.

Controversy remains surrounding liver resection for the management of intermediate HCC. Surgical procedures have been proposed by some treatment algorithms, and even patients beyond the Milan criteria have been selected for liver transplantation[56-58]. However, more evidence is needed about whether the indications should be expanded for liver resection for intermediate HCC.

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P- Reviewer: He JY, Qin JM, Romero MR, Wong GLH
S- Editor: Qiu S **L- Editor**: Wang TQ **E- Editor**: Liu SQ

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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4254/wjh.v8.i14.616

World J Hepatol 2016 May 18; 8(14): 616-624
ISSN 1948-5182 (online)

ORIGINAL ARTICLE

Observational Study

Combined acoustic radiation force impulse, aminotransferase to platelet ratio index and Forns index assessment for hepatic fibrosis grading in hepatitis B

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Supported by Shenzhen Municipal Science and Technology Innovation Fund, Nos. CXZZ20130322170220544 and JCYJ20140411112047885.

Institutional review board statement: The study was reviewed and approved by the Ethics Committee Office of Shenzhen Third People's Hospital.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: There are no conflicts of interest to report.

Data sharing statement: No additional data are available.

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Received: January 8, 2016
Peer-review started: January 8, 2016
First decision: February 26, 2016
Revised: March 8, 2016
Accepted: April 20, 2016
Article in press: April 22, 2016
Published online: May 18, 2016

Abstract

AIM: To investigate the combined diagnostic accuracy of acoustic radiation force impulse (ARFI), aspartate aminotransferase to platelet ratio index (APRI) and Forns index for a non-invasive assessment of liver fibrosis in patients with chronic hepatitis B (CHB).

METHODS: In this prospective study, 206 patients had CHB with liver fibrosis stages F0-F4 classified by METAVIR and 40 were healthy volunteers were

measured by ARFI, APRI and Forns index separately or combined as indicated.

RESULTS: ARFI, APRI or Forns index demonstrated a significant correlation with the histological stage (all $P < 0.001$). According to the AUROC of ARFI and APRI for evaluating fibrotic stages more than F2, ARFI showed an enhanced diagnostic accuracy than APRI ($P < 0.05$). The combined measurement of ARFI and APRI exhibited better accuracy than ARFI alone when evaluating $\geqslant$ F2 fibrotic stage ($Z = 2.77$, $P = 0.006$). Combination of ARFI, APRI and Forns index did not obviously improve the diagnostic accuracy compared to the combination of ARFI and APRI ($Z = 0.958$, $P = 0.338$).

CONCLUSION: ARFI + APRI showed enhanced diagnostic accuracy than ARFI or APRI alone for significant liver fibrosis and ARFI + APRI + Forns index shows the same effect with ARFI + APRI.

Key words: Acoustic radiation force impulse; Aspartate aminotransferase to platelet ratio index; Forns index; Hepatitis B virus; Non-invasive diagnosis

Core tip: Chronic hepatitis B (CHB) is a major health problem in a lot of countries all over the world, particularly in China. An accurate staging of liver fibrosis is critical for prognosticating this disease. However, although it is still the golden standard, liver biopsy is hindered by its inherent drawbacks in clinical applications. In this study, we demonstrated that non-invasive methods, including acoustic radiation force impulse (ARFI), aspartate aminotransferase to platelet ratio index (APRI) and Forns index showed significant correlations with the histological staging results from liver biopsy. The combined measurement of ARFI and APRI had the best diagnostic accuracy, which provided an ideal and convenient non-invasive diagnostic method for the detection of hepatic fibrosis of CHB patients in clinical practice.

Dong CF, Xiao J, Shan LB, Li HY, Xiong YJ, Yang GL, Liu J, Yao SM, Li SX, Le XH, Yuan J, Zhou BP, Tipoe GL, Liu YX. Combined acoustic radiation force impulse, aminotransferase to platelet ratio index and Forns index assessment for hepatic fibrosis grading in hepatitis B. *World J Hepatol* 2016; 8(14): 616-624 Available from: URL: http://www.wjgnet.com/1948-5182/full/v8/i14/616.htm DOI: http://dx.doi.org/10.4254/wjh.v8.i14.616

INTRODUCTION

Chronic liver injury, such as chronic hepatitis B (CHB), may cause inflammation and necrosis of hepatocytes, leading to hepatic fibrosis. It is a long-term pathological change with certain possibility (about 20%) of progressing to liver cirrhosis[1]. Unlike cirrhosis, hepatic fibrosis is reversible at its early stage when proper clinical therapeutic interventions are applied[2]. Therefore, an accurate staging of liver fibrosis is critical for prognosticating this disease. To date, the gold standard for staging hepatic fibrosis is still the liver biopsy, which cannot be routinely performed because of its inherent limitations, such as pain, bleeding, inaccurate staging from sampling error, and variability of biopsy interpretation[3]. During the past decades, considerable efforts have been invested in developing non-invasive methods of assessments, which may provide accurate evaluation of liver fibrosis comparable to liver biopsy. Indeed, these non-invasive methods have several advantages such as high safety margin, simple, convenient, reproducible, and inexpensive.

Acoustic radiation force impulse (ARFI) is a new quantitative assessment method of estimating tissue stiffness through measurement of shear wave velocity (SWV, measured in m/s). Its quantitative representation is named as virtual touch tissue quantification, which gives an objective numerical evaluation of the tissue stiffness[4-6]. ARFI imaging offers a quantitative assessment of the hepatic parenchyma elasticity to non-invasively grade and stage hepatic fibrosis. It has been used to diagnose hepatic fibrosis of patients with CHB[7], hepatitis C[8], cirrhosis[9], and non-alcoholic fatty liver disease (NAFLD)[10]. In addition, ARFI is often performed with serum liver functions tests [*e.g.,* alanine aminotransferase (ALT), aspartate aminotransferase (AST), total proteins, and albumin] to generate better prediction and evaluation of liver fibrosis[11]. Among these, AST platelet ratio (APRI) is a serum hepatic function test which has been proposed as a non-invasive tool for the assessment of liver fibrosis in CHB[12] or chronic hepatitis C[13]. Another important serum test is Forns index method, which uses simple obtained parameters including age, gamma-glutamyltransferase (GGT), cholesterol, and platelet count (PLT), but it requires a relatively complicated calculation[14]. One of the advantages of APRI and Forns index over the other non-invasive tests is that they are based on readily available blood tests and simple to use. Although these strategies have been widely applied in the past decade for hepatitis C evaluation[15,16], their accuracy for CHB grading are still not comparable with liver biopsy. Therefore, a combined use of these non-invasive methods may be another promising and practical diagnostic application in CHB patients. In the current study, we aimed to compare the accuracy among ARFI, APRI, Forns index and their combinations for non-invasive diagnosis grading and prognosis of human CHB-induced hepatic fibrosis.

MATERIALS AND METHODS

Subjects of study

This prospective study was approved by the ethical committee of Shenzhen Third People's Hospital. All study procedures and methods were in accordance with

the approved guidelines. All patients in this study were fully informed about the research protocol including the data handling and the privacy of personal data. After this procedure, patients signed the written consent. A total of 246 subjects were consecutively enrolled in this study, including 206 CHB subjects and 40 healthy subjects. These 206 CHB cases were selected from 245 CHB patients diagnosed by liver biopsy in Shenzhen Third People's Hospital, from May 2011 to December 2014. Of the 206 CHB patients, there were 39 female cases (18.9%) and 167 male cases (81.1%). Inclusion criteria are: (1) patients must be 18-65 years old; (2) with hepatitis B surface antigen positive for more than 6 mo; (3) without receiving antiviral treatment before this study; (4) ALT and AST were < 2 × upper limit of normal (ULN) in the past 6 mo; (5) 18.5 < body mass index (BMI) < 31.0; (6) length of liver biopsy tissue ⩾ 15 mm and contains at least 10 periportal areas; (7) hemoglobin > 90 g/L, prothrombin time 11-15.1 s; (8) activated partial thromboplastin time and thrombin time were at a normal range; and (9) cardiac and renal functions were normal. Negative for the following: Human immunodeficiency virus, hepatitis A virus, hepatitis C virus (HCV), hepatitis D virus, hepatitis E virus super-infection or co-infection, auto-immune liver diseases, alcoholic steatosis, NAFLD, hepatocellular carcinoma (HCC), pregnancy, ascites, as well as jaundice. Of the 245 eligible CHB patients, 39 were excluded because of the following: NAFLD (n = 10), received antiviral treatment before this study (n = 8), jaundice (n = 5), alcoholic steatosis (n = 6), HCV infection (n = 2), auto-immune liver disease (n = 1), with age < 18 (n = 4), with age > 65 (n = 1), and declined to participate (n = 2). Healthy group consisted of 40 volunteers, with 30 males and 10 females, aged range from 20-53 years old, with mean age of 39.8 ± 11.45 years and no hepatitis B virus (HBV) or HCV infection, no hypertension, diabetes, fatty liver and other apparent diseases. The BMI of healthy subjects were between 18.5 and 31.0. Other parameters were similar to the CHB patients. All CHB patients were examined by ARFI one day before or on the day of liver biopsy. All the subjects had blood or sera drawn for the detection of platelet and fibrotic serological markers.

Liver biopsy and pathological staging

Liver biopsy tissue specimens were collected by needle puncture (MN1613, Bard Biopsy Systems, Tempe, AZ) under the Color Doppler Ultrasound guidance in a separate clinic setting for diagnostic purposes. The liver specimen was 15-20 mm in length, including at least 10 portal vein areas. Then it was embedded by paraffin and stained by Sirius Red (Sigma-Aldrich, St. Louis, MO). Liver fibrosis stage was assessed by the METAVIR scoring system (F0 = no fibrosis; F1 = portal fibrosis without septa; F2 = portal fibrosis and a few septa; F3 = numerous fibrosis without cirrhosis; and F4 = cirrhosis)[17]. The METAVIR scoring system was previously used in other reports on CHB[18,19]. Two independent pathologists were responsible for the staging of all samples without additional information about the specimens they checked.

ARFI

The detection of ARFI in the liver was performed under fasting conditions using Siemens Acuson S2000 with probe detector 4C1, frequency 2.0-4.0 MHz (Siemens Healthcare, Erlangen, Germany) according to routine instructions. ARFI was mainly conducted by a radiologist (Dong CF) with assistant from another physician and a nurse. Dong CF has 11-year experience in clinical radiology and 4-year experience in ARFI diagnosis. Form of the liver capsule and the echogenicity of hepatic parenchyma were recorded. Detection of SWV (m/s) of hepatic segments s5, s6, s7 and s8 was repeated for 3 times and the mean values were calculated. Thus, 12 measurements of hepatic segments s5, s6, s7, s8 were recorded. Our pilot study in healthy volunteers showed that when compared with conventional ARFI protocol (mean value from 10 measurements), the current protocol exhibited similar results with smaller standard deviation (1.08 ± 0.21 m/s *vs* 1.11 ± 0.12 m/s; t = 0.6794, P > 0.05). This is consistent with a report that showed the reproducibility of measurements in the right lobe was higher[20]. Images and data of ARFI were saved for analysis.

Blood markers for APRI and Forns index evaluations

AST was determined in the same laboratory prior to the liver biopsy using Siemens ADVIA 2400 Chemistry system (Siemens Healthcare). Enzymatic activity was measured at 37 ℃, according to International Federation of Clinical Chemistry standards. Platelet count was assessed by an automatic blood cell analyzer (XE-5000 Automated Hematology System, Sysmex, Lincolnshire, IL). The ULN range of AST was considered as 40 U/L.

$$\text{APRI} = \text{AST}(/\text{ULN})/\text{PLT}(10^9/\text{L}) \times 100.$$

$$\text{Forns index} = 7.811 - 3.131 \times \text{Ln}(\text{PLT}) + 0.781 \times \text{Ln}(\text{GGT}) + 3.467 \times \text{Ln}(\text{age}) - 0.014 \times (\text{cholesterol})$$

Combined assessments of ARFI + APRI/ARFI + Forns index

A logistic regression analysis model for hepatic fibrosis ⩾ F2 has been established by using the ENTER method.

Statistical analysis

Continuous normal distribution data were represented with means ± SD. Categorical normal distribution data were represented with median ± quartile (M ± Q). Kruskal-Wallis test was used to analyze the differences among these different groups. When there was a statistical significance (P < 0.05), a post-hoc Bonferroni test was applied to analyze data between two groups. P < 0.05 was considered to be statistically significant using a SPSS 13.0, IBM, Armonk, NY. The box plot was used to record the mean and degree of variation. MedCalc software (Ostend, Belgium) was used to draw receiver operating characteristic curve (ROC) and calculate cut-off value, sensitivity, specificity, positive predictive

Table 1 Results of basic information and acoustic radiation force impulse/aspartate aminotransferase to platelet ratio index/Forns index of all examinees

Group	Age (yr)	Gender (male/female)	BMI	ARFI	APRI	Forns index
F0 (n = 40)	39.8 ± 11.45	30/10	22.91 ± 2.31	1.09 (1.01, 1.21)	0.19 (0.14, 0.28)	5.58 ± 1.33
F1 (n = 41)	33.07 ± 7.97[1]	33/8	22.37 ± 2.24	1.19 (1.15, 1.28)[1]	0.34 (0.28, 0.44)[1]	5.60 ± 1.19
F2 (n = 52)	38.27 ± 7.66[2]	43/9	22.26 ± 2.41	1.31 (1.21, 1.43)[1,2]	0.42 (0.32, 0.64)[1]	6.73 ± 1.09[1,2]
F3 (n = 59)	39.83 ± 8.73[2]	47/12	22.44 ± 2.57	1.52 (1.35, 1.64)[1,2,3]	0.45 (0.32, 0.86)[1,2]	7.58 ± 1.55[1,2,3]
F4 (n = 54)	43.85 ± 10.81[1,2,3,4]	44/10	22.35 ± 2.47	1.92 (1.74, 2.14)[1,2,3,4]	0.80 (0.51, 1.68)[1,2,3,4]	9.43 ± 2.30[1,2,3,4]
χ^2/F	7.907	0.947	0.477	176.043	107.992	49.501
P value	< 0.001	0.918	0.753	< 0.001	< 0.001	< 0.001

For age and Forns index, data were represented in mean ± SD. For ARFI and APRI data, results were exhibited in median ± quartile. [1]Means significant change against the F0 group; [2]Means significant change against the F1 group; [3]Means significant change against the F2 group; [4]Means significant change against the F3 group. For gender, ARFI and APRI comparisons, size of test $\alpha' = \alpha/n = 0.005$; for age and Forns index comparison, size of test $\alpha = 0.05$. ARFI: Acoustic radiation force impulse; APRI: Aspartate aminotransferase to platelet ratio index; BMI: Body mass index.

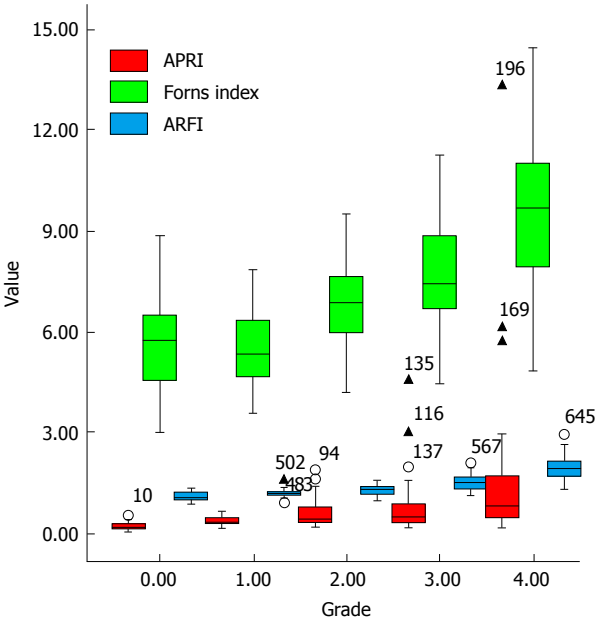

Figure 1 Box plots show correlation between noninvasive tests and histological stages from liver biopsy. Top and bottom of boxes represent first and third quartiles, respectively. Length of box represents interquartile range within which 50% of values are located. Line through each box represents median. Error bars mark the minimum and maximum values (range). Small circles represent the outliers. Triangles represent the extreme value, which is > 3 × interquartile range. ARFI: Acoustic radiation force impulse; APRI: Aspartate transaminase to platelet ratio index.

values, negative predictive values, AUROC of ARFI and APRI for every liver fibrotic stage. The ROC curve of two variables combination (ARFI + APRI and ARFI + Forns index) and three variables combination (ARFI + APRI + Forns index) for significant hepatic fibrosis (≥ F2) was also analyzed. When AUROC > 0.5, the closer of AUROC to 1, the better diagnostic outcome it provided. Comparison of AUROC among these parameters and their combination was analyzed by the Delong test[21].

RESULTS

Results of basic information, ARFI, APRI, and Forns index

Basic information (*e.g.*, age and gender) and assessment results of ARFI, APRI, and Forns index of all subjects were shown in Table 1. The average ages of subjects with significant or serious fibrosis (F2, F3 and F4) were significantly higher than subjects with mild fibrosis (F1) (P = 0.009 for F2 *vs* F3, P < 0.001 for F2 *vs* F4, and P < 0.001 for F3 *vs* F4). Also, male patients showed higher incidence of hepatic fibrosis (from F1 to F4) than female patients. The differences of ARFI results among F0, F1, F2, F3 and F4 groups were significant (P < 0.05). For Forns index, except for F0 and F1 group, the differences among other groups were significant (P < 0.05). Results of APRI indicated that only F4 showed significant change from other groups (F0, F1, F2 and F3) (all P < 0.001), while the F1, F2, and F3 groups showed significantly higher values than the F0 group (all P < 0.001) (Table 1).

Correlations between ARFI, APRI, Forns index and hepatic pathology

The median, quartile, minimum value, maximum value and outlier of ARFI, APRI and Forns index were shown in box type image (Figure 1). There was a high correlation between the staging of ARFI/APRI/Forns index and the hepatic histology, with correlation coefficient 0.845 (P < 0.001), 0.641 (P < 0.001) and 0.644 (P < 0.001), respectively (Table 2). In ENTER model, Y axis was the result from liver biopsy and the X axis was the results from ARFI + APRI or ARFI + Forns Index combined assessments. The equation for ARFI + APRI was y = -13.27 + 9.11 ARFI + 5.03 APRI, while the equation for ARFI + Forns index was y = -15.08 + 8.67 ARFI + 0.70 Forns index.

Determination of the cut-off values of hepatic fibrosis staging

There were significantly different interval ranges between different liver fibrotic stages and the corresponding ARFI and APRI results. In order to determine the cut-off value of each fibrotic stage, we applied ROC to analyze the data from both ARFI and APRI (Figure 2). From the result, it showed that the diagnostic performance of ARFI for predicting stages more than F2, F3 and F4 was 91% (95%CI: AUROC = 0.87-0.95, P < 0.05), 94% (95%CI:

Table 2 Correlations of non-invasive tests with histological fibrosis stage by rank correlation analysis

Histological staging	Noninvasive test	Correlation (Spearman coefficient)	95%CI	*P* value
METAVIR classification	ARFI	0.845	0.805-0.877	< 0.001
	APRI	0.641	0.561-0.709	< 0.001
	Forns index	0.644	0.564-0.711	< 0.001

ARFI: Acoustic radiation force impulse; APRI: Aspartate aminotransferase to platelet ratio index.

Table 3 Cut-off values of acoustic radiation force impulse and aspartate aminotransferase to platelet ratio index for the diagnosis of liver fibrosis (95%CI)

	⩾ F1	⩾ F2	⩾ F3	F4
ARFI				
Cut-off (m/s)	1.26	1.29	1.43	1.62
Sensitivity	76.2% (69.80-81.90)	83.6% (77.10-88.90)	82.3% (74.00-88.80)	90.7% (79.70-96.90)
Specificity	95.0% (83.10-99.40)	90.1% (89.50-97.60)	89.5% (83.00-94.10)	92.2% (87.40-95.60)
PPV	99.1% (96.20-99.90)	94.5% (91.90-99.10)	86.9% (79.10-92.70)	76.0% (64.40-86.30)
NPV	35.9% (22.50-47.40)	73.0% (63.10-81.40)	85.6% (78.60-91.00)	97.2% (93.70-99.10)
AUROC	0.90 (0.86-0.94)[a]	0.91 (0.87-0.95)[a]	0.94 (0.90-0.96)[a]	0.96 (0.93-0.98)[a]
APRI				
Cut-off (m/s)	0.30	0.41	0.49	0.44
Sensitivity	84.0% (78.20-88.70)	68.5% (60.80-75.50)	63.7% (54.10-72.60)	83.3% (70.70-92.10)
Specificity	85.0% (70.20-94.30)	82.7% (72.70-90.20)	79.7% (71.90-86.20)	67.2% (70.10-73.80)
PPV	97.6% (94.20-99.30)	89.0% (82.20-93.80)	72.8% (62.90-81.20)	41.7% (32.30-51.60)
NPV	42.7% (30.00-56.10)	56.3% (46.80-65.40)	72.1% (64.00-79.20)	93.5% (87.90-97.00)
AUROC	0.92 (0.88-0.95)[a]	0.84 (0.79-0.89)[a]	0.79 (0.73-0.84)[a]	0.82 (0.76-0.86)[a]

[a]$P < 0.05$ for all values. ARFI: Acoustic radiation force impulse; APRI: Aspartate aminotransferase to platelet ratio index; AUCROC: Area under the receiver operating characteristic curve; NPV: Negative predictive value; PPV: Positive predictive value.

Table 4 Binary logistic regression of two variables in hepatic fibrosis ⩾ F2

Combination	Variable	RC	SD of RC	Wald	*P* value	OR	95%CI of OR
ARFI + APRI	ARFI	9.11	1.48	37.68	< 0.001	9085.54	494.92-166789.07
	APRI	5.03	1.30	15.07	< 0.001	153.01	12.07-1939.04
	Constant	-13.27	1.95	46.09	< 0.001	-	-
ARFI + Forns index	ARFI	8.67	1.44	36.16	< 0.001	5824.00	345.12-98280.97
	Forns index	0.70	0.17	16.27	< 0.001	2.01	1.43-2.82
	Constant	-15.08	2.08	52.68	< 0.001	-	-

ARFI: Acoustic radiation force impulse; APRI: Aspartate aminotransferase to platelet ratio index; OR: Odds ratio; RC: Regression coefficient.

AUROC = 0.90-0.96, $P < 0.05$), 96% (95%CI: AUROC = 0.93-0.98, $P < 0.05$), and the best cut-off value of F2, F3 and F4 was 1.29, 1.43 and 1.62 m/s. However, APRI measurement showed decreased accuracy of diagnosing significant fibrosis when compared with ARFI (Table 3).

Combined assessment of ARFI + APRI/ARFI + Forns index/ARFI + APRI + Forns index for hepatic fibrosis ⩾ F2

Firstly we established a logistic regression analysis model for hepatic fibrosis ⩾ F2 in which the Y axis was the result from liver biopsy and the X axis was the results from combined ARFI + APRI/ARFI + Forns index assessment (Table 4). From the AUROC results of Table 5, when evaluating patients with hepatic fibrosis ⩾ F2, there was a significant change between the AUROCs of ARFI + APRI and ARFI alone (0.940 and 0.913, respectively; Z = 2.77, $P = 0.006$), also between ARFI + Forns index and ARFI alone (0.933 and 0.913, respectively; Z = 2.091, $P = 0.037$), ARFI + APRI + Forns index and ARFI alone (0.944 and 0.913, respectively; Z = 2.893, $P = 0.004$), indicating an enhanced screening ability of the combined assessment than ARFI alone. However, the change between ARFI + APRI and ARFI + APRI + Forns index was not significant (0.940 and 0.944, respectively; Z = 0.958, $P = 0.338$), suggesting that Forns index cannot further improve the diagnostic accuracy for staging hepatic fibrosis ⩾ F2 when using a combined method of ARFI + APRI (Figure 3).

DISCUSSION

To date, the gold standard for the diagnosis of liver fibrosis remains to be liver biopsy. In most circumstances, patients find it difficult to accept liver biopsy due

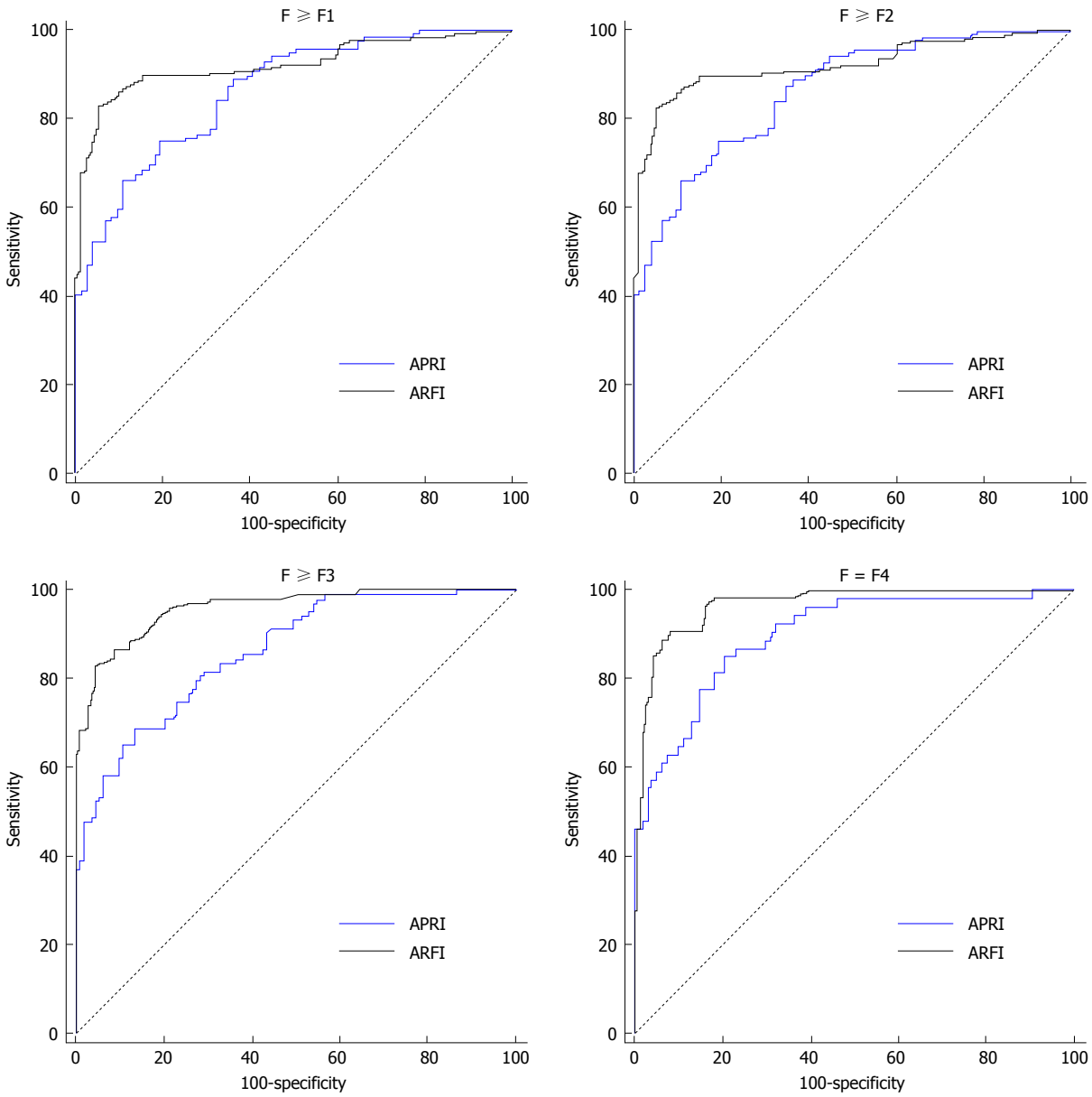

Figure 2 Receiver operating characteristic curves for acoustic radiation force impulse and aspartate transaminase to platelet ratio index for diagnosis of hepatic fibrosis (F1-F4). ARFI: Acoustic radiation force impulse; APRI: Aspartate transaminase to platelet ratio index.

to its complications. From 2009, with the introduction of ARFI, the clinical research on non-invasive assessment of fibrosis rapidly progressed. As an advanced imaging technology, ARFI is capable of providing biomechanical information on the tissue stiffness and elasticity using conventional ultrasound scanning of anatomical location and structure[22,23]. However, its utility, particularly in combination with other non-invasive methods in hepatitis B, has not been adequately evaluated.

In the current study, CHB patients with different stages of liver fibrosis were diagnosed by ARFI, APRI, Forns index and their combined assessments. Our results demonstrated that the mean SWV value from ARFI was highly correlated with the staging of liver fibrosis classified by liver biopsy (METAVIR classification). This result indicated that biomechanical properties (*e.g.*, hepatic elasticity and stiffness) had progressed from liver fibrosis to cirrhosis during the development of CHB, which was consistent with the pathological progression of hepatocyte degeneration, necrosis, inflammation reaction, hepatocyte regeneration, formation of connective tissue fiber intervals, and liver lobule structural failure during the course of liver fibrosis of HBV infection[24].

With the progression of liver fibrosis from F2 to F4, the effectiveness of ARFI on the diagnosis of liver fibrosis also increased. That is, when the value of SWV was lower than 1.29 m/s (clinically F0 and F1 patients), hepatic fibrosis could be unlikely significant. SWV higher than 1.43 m/s could be likely considered as an indication for serious liver fibrosis (F3, sensitivity 82.3% and specificity 89.5%), and SWV > 1.62 m/s could be diagnosed as early cirrhosis (F4, sensitivity 90.7% and specificity 92.2%). In addition, when they were used

Table 5 Comparing area under the receiver operating characteristic curve of acoustic radiation force impulse/acoustic radiation force impulse + aspartate aminotransferase to platelet ratio index/acoustic radiation force impulse + Forns index/acoustic radiation force impulse + aspartate aminotransferase to platelet ratio index + Forns index in patients with fibrosis stage ≥ F2

Comparison	AUROC	Difference	95%CI		Z	*P* value
			Lower limit	Upper limit		
ARFI	0.913	0.027	0.008	0.046	2.770	0.006
ARFI + APRI	0.940					
ARFI	0.913	0.020	0.001	0.040	2.091	0.037
ARFI + Forns index	0.933					
ARFI	0.913	0.031	0.010	0.053	2.893	0.004
ARFI + APRI + Forns index	0.944					
ARFI + APRI	0.940	0.007	-0.011	0.025	0.728	0.466
ARFI + Forns index	0.933					
ARFI + APRI	0.940	0.005	-0.005	0.014	0.958	0.338
ARFI + APRI + Forns index	0.944					
ARFI + Forns index	0.933	0.011	-0.001	0.023	1.789	0.074
ARFI + APRI + Forns index	0.944					

AUROC: Area under the receiver operating characteristic curve; ARFI: Acoustic radiation force impulse; APRI: Aspartate aminotransferase to platelet ratio index.

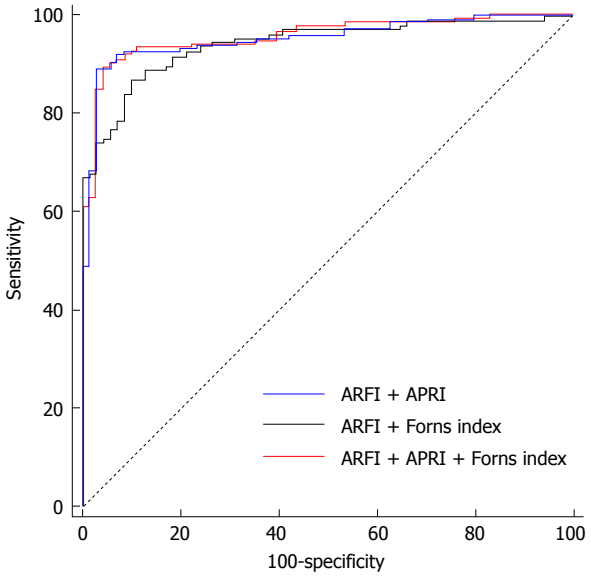

Figure 3 Receiver operating characteristic curves of acoustic radiation force impulse + aspartate transaminase to platelet ratio index/acoustic radiation force impulse + Forns index/ acoustic radiation force impulse + aspartate transaminase to platelet ratio index + Forns index assessment for the diagnosis of liver fibrosis ≥ F2 in patient with chronic hepatitis B. ARFI: Acoustic radiation force impulse; APRI: Aspartate transaminase to platelet ratio index.

independently, ARFI was the best way for the diagnosis of fibrosis ≥ F2; ARFI provides a dynamic technical support for non-invasive diagnosis of liver fibrosis. This result is in line with a report found that ARFI correlated well with liver biopsy and thus was a reliable ultrasound-based method for the assessment of advanced fibrosis induced by CHB[25].

Currently it is difficult for non-invasive diagnostic methods to differentiate F0 and F1 fibrotic stages. However, in this study, we found that there was a significant change of ARFI readings between the F0 and F1 groups (Table 1). It is known that stage F2 possesses significant diagnostic value in determining the progression of liver disease and anti-viral therapy choice. At this stage, patients have more risk in developing complications such as portal hypertension, cirrhosis, and HCC than patients without significant liver fibrosis[26]. If patients receive anti-viral therapy promptly during this period, it is possible to retard or even reverse the pathological progression of fibrosis[27]. Thus, early accurate diagnosis and appropriate therapy to patients at F2 fibrosis evidently decreases the morbidity and mortality of patients with CHB[28,29].

Similar to the FibroScan method which is partially affected by obesity[30], ARFI also has some disadvantages. For example, certain hepatic disorders (*e.g.*, ascites and acute icteric hepatitis) may affect the ARFI results. However, in our study, all the enrolled subjects including obese patients with BMI of 30.81 successfully got SWV values. Thus, ARFI may have a wider application range than FibroScan. In general, ARFI overcome a spectrum of disadvantages of conventional ultrasound technologies, such as no manual operation of pressing, improved depth limitation (5 cm of the earlier machines and 8 cm of the newer machines) and location of imaging. Compared to other methods, ARFI has no pain, with good reproducibility of data and simple operation. Indeed, ARFI is potentially limited by patients with a BMI > 40 or after contrast-enhanced ultrasonography. Thus, its combination with other non-invasive methods is necessary to enhance the diagnostic accuracy[31].

Currently, serological diagnostic assays for non-invasive assessment of liver fibrosis are available including direct and indirect methods. The main purpose of these methods is to identify the existence of fibrosis but not the grading or staging. In this study, APRI and Forns index were also used to stage liver fibrotic stage. Although the sensitivity and specificity of these methods for the diagnosis of liver fibrosis was lower than ARFI,

they partially reflected the pro-inflammatory response and hepatic compensation. The most important finding of this study was that combined measurement of ARFI and APRI exhibited better accuracy than ARFI or APRI alone when evaluating ⩾ F2 fibrosis stage. Combination of ARFI, APRI and Forns index did not further improve the diagnostic effect than the combination of ARFI and APRI.

In conclusion, ARFI, APRI and Forns index correlated well with the histological liver fibrosis stages in CHB patients. ARFI showed better accuracy than APRI when evaluating F2, F3 and F4 stages. Combined check with ARFI and APRI showed a significant enhancement of diagnostic accuracy than ARFI or APRI alone. ARFI + APRI exhibited similar enhancement of diagnostic accuracy of hepatic fibrosis with ARFI + APRI + Forns index when evaluating fibrotic stages more than F2 in CHB patients. This study provides an ideal and convenient non-invasive diagnostic method for the detection of hepatic fibrosis of CHB patients in clinical practice.

COMMENTS

Background

Hepatitis B virus (HBV) infection-mediated chronic injury of hepatocytes induces fibrosis, which may progress to end-stage liver diseases like cirrhosis and hepatocellular carcinoma. Thus, accurate grading of hepatic fibrosis is important for the application of appropriate intervening strategy to retard the progression. To date, the "golden standard" of fibrotic grading is still liver biopsy, which wide clinical application is hindered by its inherent drawbacks. In recent years, biomechanical-based ultrasonic elastography received mass attention. However, several clinical studies found that the sole application of ultrasonic elastography may bring evident errors in diagnosing hepatic fibrosis. It is suggested that a combination of ultrasonic elastography and serum liver functions tests holds the potential to overcome those disadvantages.

Research frontiers

There are an increasing number of hospitals using non-invasive ultrasonic elastography techniques, such as acoustic radiation force impulse (ARFI) and Fibroscan to grade hepatic fibrosis of chronic hepatitis B (CHB) patients in China and chronic hepatitis C patients in Western countries. Combination of different ultrasonic elastography techniques has been reported by a number of reports. However, few studies investigate the accuracy of the combination of ultrasonic elastography and serum liver functions tests.

Innovations and breakthroughs

This study evaluated the accuracy of one ultrasound elastography method (ARFI) and two serum biochemical tests [aspartate aminotransferase to platelet ratio index (APRI) and Forns index], as well as their combination in the assessment of liver fibrosis in CHB. The authors found that ARFI + APRI exhibited similar enhancement of diagnostic accuracy of hepatic fibrosis with ARFI + APRI + Forns index when evaluating fibrotic stages more than F2 in CHB patients.

Applications

The data in this study suggest that doctor can yield favorable outcomes through the accumulation of technical experience. Furthermore, this study also provides readers with important information regarding an ideal and convenient non-invasive diagnostic method for the grading of hepatic fibrosis of CHB patients.

Terminology

ARFI imaging involves mechanically exciting a localized region of interest in the tissue with acoustic radiation force to induce a shear wave in the tissue. The displacement of the shear wave is tracked using a pulse-echo mode ultrasound at several lateral locations along the propagation path of the shear wave. By measuring the time to peak displacement at each location, the shear wave velocity was calculated, which is directly related to the elasticity of the tissue. APRI = AST(/ULN)/PLT(109/L) × 100. Forns index = 7.811 - 3.131 × Ln(PLT) + 0.781 × Ln(GGT) + 3.467 × Ln(age) - 0.014 × (cholesterol).

Peer-review

This is a good attempt by Dong *et al* to compare ARF1, APR1 and Forns to determine fibrosis stage in chronic HBV patients. As these are not new techniques for fibrosis evaluation and they wanted to establish that combination of ARF1/ APRI and ARF1/ Forns as better non-invasive technique.

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DOI: 10.4254/wjh.v8.i14.625

World J Hepatol 2016 May 18; 8(14): 625-631
ISSN 1948-5182 (online)

ORIGINAL ARTICLE

Randomized Clinical Trial

Co-treatment with pegylated interferon alfa-2a and entecavir for hepatitis D: A randomized trial

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Author contributions: Abbas Z was responsible for the study conception and design, data analysis and interpretation, and manuscript drafting; Abbas Z and Memon MS recruited patients for the study; Umer MA, Abbas M and Shazi L coordinated study related activities and helped in manuscript drafting; all authors reviewed and approved the final version to be submitted for publication.

Institutional review board statement: The study was approved by Independent Ethics Review Board and Institutional Review Board.

Clinical trial registration statement: This investigator initiated trial was registered with the Roche (ML25746).

Informed consent statement: All study participants provided informed written consent prior to study enrollment.

Conflict-of-interest statement: Authors do not have any conflict of interest to declare.

Data sharing statement: No additional data are available.

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Received: January 25, 2016
Peer-review started: January 27, 2016
First decision: March 9, 2016
Revised: March 30, 2016
Accepted: April 14, 2016
Article in press: April 18, 2016
Published online: May 18, 2016

Abstract

AIM: To investigate the efficacy of pegylated interferon alfa (PEG-IFNα) therapy with and without entecavir in patients with chronic hepatitis D.

METHODS: Forty hepatitis D virus (HDV) RNA positive patients were randomized to receive either PEG-IFNα-2a 180 μg weekly in combination with entecavir 0.5 mg daily (n = 21) or PEG-IFNα alone (n =19). Patients who failed to show 2 log reduction in HDV RNA level at 24 wk of treatment, or had detectable HDV RNA at 48 wk of therapy were considered as treatment failure. Treatment was continued for 72 wk in the rest of the patients. All the patients were followed for 24 wk post treatment. Intention to treat analysis was performed.

RESULTS: The mean age of the patients was 26.7 ± 6.8 years, 31 were male. Two log reduction in HDV RNA levels at 24 wk of therapy was achieved in 9 (43%) patients receiving combination therapy and 12 (63%) patients receiving PEG-IFNα alone (P = 0.199). Decline in hepatitis B surface antigen (HBsAg) levels was insignificant. At the end of treatment, HDV RNA was negative in 8 patients (38%) receiving combination

therapy and 10 patients (53%) receiving PEG-IFNα-2a alone. Virological response persisted in 7 (33%) and 8 (42%) patients, respectively at the end of the 24 wk follow-up period. One responder patient in the combination arm lost HBsAg and became hepatitis B surface antibody positive. Six out of 14 baseline hepatitis B e antigen reactive patients seroconverted and four of these seroconverted patients had persistent HDV RNA clearance.

CONCLUSION: Administration of PEG-IFNα-2a with or without entecavir, resulted in persistent HDV RNA clearance in 37% of patients. The addition of entecavir did not improve the overall response.

Key words: Hepatitis D; Entecavir; Hepatitis B surface antigen; Pegylated interferon; Hepatitis D virus RNA; Treatment

Core tip: Chronic hepatitis D is a difficult to treat infection. Six months post treatment response is seen only in one quarter of the patients treated with pegylated interferon alfa (PEG-IFNα). In an attempt to improve the response of PEG-IFN, we combined entecavir. This is the first study to evaluate the efficacy of PEG-IFN with entecavir compared to PEG-IFN alone for the treatment of hepatitis D infection. Our study showed that the combination treatment did not have any additional benefit in terms of hepatitis D virus RNA suppression and hepatitis B surface antigen reduction as compared to PEG-IFN alone.

Abbas Z, Memon MS, Umer MA, Abbas M, Shazi L. Co-treatment with pegylated interferon alfa-2a and entecavir for hepatitis D: A randomized trial. *World J Hepatol* 2016; 8(14): 625-631 Available from: URL: http://www.wjgnet.com/1948-5182/full/v8/i14/625.htm DOI: http://dx.doi.org/10.4254/wjh.v8.i14.625

INTRODUCTION

The prevalence of hepatitis B surface antigen (HBsAg) positive individuals in Pakistan is 2.5%[1] and it is estimated that 5 million persons are HBsAg positive. In a large series, hepatitis D virus (HDV) antibodies in HBsAg positive individuals were found to be present in 16.6% cases[2]. So there is a large pool of patients exposed to hepatitis D in this country.

Chronic hepatitis D is a difficult to treat infection. Standard interferon-alfa is not an ideal treatment[3]. Recent few trials with pegylated interferon alfa (PEG-IFNα) have shown a better response of 25%-30% six months post treatment[4,5]. In an attempt to improve the response of PEG-IFNα, the International Hepatitis Delta Network evaluated adefovir and later tenofovir in combination with PEG-IFNα in HIDIT-1 and HIDIT-2 studies[6,7]. It was expected that HIDIT-2 will yield better results due to use of potent nucleotide analogue in combination with PEG-IFNα for a longer duration of therapy.

Recently presented results of HITID-2 trial[7] showed that 96 wk of PEG-IFNα-2a and tenofovir therapy was associated with a high frequency of serious adverse events. Combination treatment had similar effects on HBsAg reduction as compared to PEG-IFNα alone. More than one third of the on-treatment responders experienced a posttreatment HDV RNA relapse despite prolonged therapy. The results of the long term post treatment follow-up are awaited. Combination therapy with tenofovir did not provide obvious benefits in hepatitis D patients with low baseline hepatitis B virus (HBV)-DNA levels and prolongation of treatment to 96 wk did not provide higher off-treatment HDV RNA responses (compared to 48 wk in the HIDIT-1 study).

The aim of this study is to evaluate the efficacy of PEG-IFNα-2a with entecavir for the treatment of chronic hepatitis D. The reason for choosing entecavir was that HIDIT-2 study using tenofovir was in progress with high hopes and no data was available for entecavir in combination with PEG-IFNα-2a in the chronic hepatitis D setting. This drug, particularly in combination with PEG-IFNα-2a, have shown good results in HBsAg decline[8].

MATERIALS AND METHODS

Trial design

This randomized study compared the efficacy of PEG-IFNα-2a plus entecavir *vs* PEG-IFNα-2a alone for the treatment of chronic hepatitis D. Patients were randomized 1:1 into two groups. Duration of treatment was 72 wk with a post-treatment follow-up of 24 wk.

Participants

Inclusion criteria were age 15-60 years, anti-HDV anti body positive and detectable serum HDV RNA at enrolment by real time polymerase chain reaction (PCR), elevated alanine aminotransferase (ALT) on two occasions in last 3 mo during screening phase, patients with compensated liver disease, *i.e.,* Child Pugh class A, hemoglobin > 12.0 g/dL for males and > 11.0 g/dL for females at screening, total leucocyte count > 3.000/mm^3, and neutrophils > 1500/mm^3, platelets > 80.000/mm^3, serum creatinine level < 1.5 mg/dL and liver biopsy within 6 mo prior to randomization.

Exclusion criteria were patients who had received therapy for chronic hepatitis D, co-infection with hepatitis C or human immunodeficiency virus, serum total bilirubin greater than twice the upper limit of normal at screening, evidence of decompensated liver disease (Childs B-C), history or other evidence of a medical condition associated with chronic liver disease (*e.g.*, Wilson's disease, hemochromatosis, autoimmune hepatitis, alcoholic liver disease, alpha1 anti-trypsin deficiency, toxin exposures, thalassemia), women with ongoing pregnancy or who are breast feeding, evidence of drug

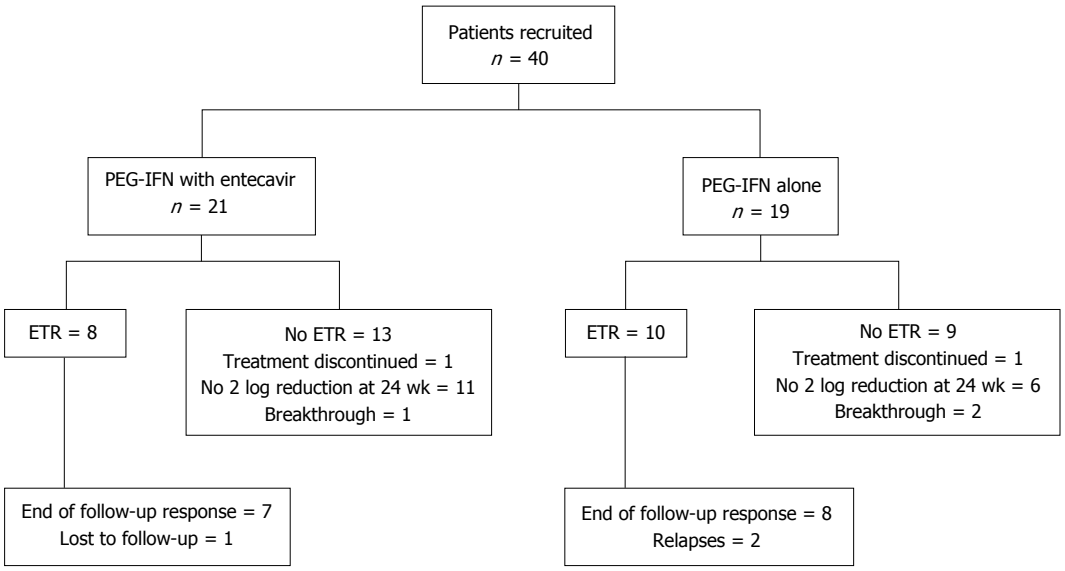

Figure 1 Flow diagram of study patients. PEG-IFN: Pegylated interferon; ETR: End of treatment response.

and/or alcohol abuse, history of severe cardiac or pulmonary disease, inability or unwillingness to provide informed consent or abide by the requirements of the study.

Settings

The study was conducted at the Orthopaedic and Medical Institute, Karachi, Liver Stomach Clinic, Karachi and Asian Institute of Medical Sciences, Hyderabad, Pakistan. The study was conducted in accordance with the guidelines of the Declaration of Helsinki and principles of Good Clinical Practice. Patients gave the informed consent and the ethics committee approved the study.

Interventions

The dose of PEG-IFNα-2a in each arm was 180 μg weekly (Pegasys®, F. Hoffmann-La Roche Ltd, Basel). Entecavir was given in a dose of 0.5 mg per oral daily in the combination arm.

Outcomes

Virological response was defined as HDV RNA clearance at the end of treatment and at follow-up six months post treatment. Biochemical response was normalization of ALT at the end of treatment and at follow-up.

Treatment failure was defined as failure to show 2 log reduction in HDV RNA level at 24 wk of treatment, or presence of detectable HDV RNA at 48 wk of therapy or relapse at 24 wk post treatment follow-up. Development of decompensation (ascites or hepatic encephalopathy) during the treatment, drop outs, and lost to follow-up were also considered as treatment failure in an intention to treat analysis (Figure 1).

Randomization

Randomization (1:1 allocation) was computer-generated. The investigators were not involved in sequence generation or allocation concealment steps and were provided with sealed envelopes containing the treatment code to administer, in increasing numbers, according to chronological inclusion in the study.

Viral nucleic acids and serologic testing

Viral nucleic acids were isolated from patients' serum samples by High Pure Viral Nucleic Acid Kit, according to the manufacturer's instructions (Roche Diagnostics, United States). Serum HBV DNA levels were measured using the Cobas TaqMan (Roche Diagnostics Systems, Basel, Switzerland) with a lower limit of quantification 20 IU/mL. For HDV RNA, qualitative test was based on the reverse transcription PCR of the target gene. Quantification of HDV RNA was done by real time PCR having a lower limit of detection of 500 IU/mL. Hepatitis B e antigen (HBeAg) and antibody against HBeAg (anti-HBe) status was determined using enzyme immunoassays. Serum HBsAg was quantified using the Architect HBsAg assay (Abbott Laboratories, Abbott Park, IL, United States). Grading of inflammation and the staging of fibrosis was performed according to the Batt's and Ludwig's classification[9].

On-treatment evaluation

The Patients were educated regarding administration of subcutaneous pegylated interferon and oral entecavir, expected adverse events, schedule for laboratory monitoring, and clinic appointment. Patients were evaluated as outpatients for safety, tolerance and efficacy every 4 wk during treatment until week 72 and then at 92 wk, *i.e.,* 24 wk post treatment during the follow-up period. At each visit complete blood count and biochemistry was assessed. HDV RNA levels were measured at baseline, 24, 48, 72 and 96 wk. HBsAg levels were measured at baseline and 24 wk. HBeAg and anti-HBe antibodies were checked at baseline. In case of HBeAg reactive, tests for HBeAg and anti-HBeAg

Table 1 Baseline characteristics of study patients *n* (%)

	PEG-IFNα with entecavir (*n* = 21)	PEG-IFNα alone (*n* = 19)	*P* value
Age (mean, yr)	26.4 ± 6.4	27 ± 7.4	0.946
Gender (male:female)	16:5	15:4	1.00
Body mass index (kg/m^2)	21.8 ± 3.6	23.6 ± 4.3	0.151
Hemoglobin (g/dL)	13.7 ± 1.59	13.9 ± 1.3	0.473
Total leucocyte count (× 10^6/L)	7.1 ± 2.0	6.7 ± 1.9	0.626
Platelets count (× 10^9/L)	237 ± 83	185 ± 59	0.023[1]
Total bilirubin (mg/dL)	0.67 ± 0.34	0.70 ± 0.38	0.828
ALT (IU/L)	87 ± 55	89 ± 41	0.379
GGT (IU/L)	49 ± 41	69 ± 72	0.255
Inflammatory grade on biopsy			0.186
0-1	5 (31)	1 (5)	
2-3	16 (69)	18 (95)	
Fibrosis stage on biopsy			0.105
0-2	12 (57)	6 (32)	
3-4	9 (43)	13 (68)	
Cirrhosis	2 (10)	6 (32)	0.120
HBeAg reactive	7 (33)	7 (37)	0.816
HDV RNA (mean log10 IU/mL)	7.5 ± 1.1	6.9 ± 1.2	0.119
HBV DNA detected	5 (24)	5 (26)	1.00
HBV DNA (mean log10 IU/mL)	1.08 ± 2.10	1.48 ± 2.70	0.656
HBsAg (mean log10 IU/mL)	4.50 ± 0.42	4.20 ± 0.64	0.068

[1]Significant *P* value. ALT: Alanine aminotransferase; GGT: Gamma glutamyl transferase; HBeAg: Hepatitis B e antigen; HDV: Hepatitis D virus; HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen; PEG-IFNα: Pegylated interferon alfa.

done were checked at 24, 48 and 72 wk to document seroconversion.

Adverse events

Adverse events and clinical laboratory parameters were recorded. Serious adverse events were defined as those that were fatal, life-threatening, required inpatient hospitalization or discontinuation of treatment. These included decompensation of liver disease and mortality. Non-serious adverse events and laboratory abnormalities leading to dose modifications and premature withdrawal from therapy were noted.

Statistical analysis

Data were expressed as the number of subjects with percentages for nominal variables. These variables were compared by χ^2 or Fisher exact test. Continuous variables were presented as mean (standard deviation), and compared using Mann-Whitney *U* test. The degree of the relationship between linear related variables was measured by the Pearson *r* correlation test. Statistical analyses were performed using SPSS 20.0 software (IBM SPSS Statistics, New York, NY, United States). All tests were 2-tailed and a two-tailed *P* value < 0.05 was required for statistical significance. Intention-to-treat analysis was done to include all randomized patients.

RESULTS

A total of 40 patients with chronic hepatitis D was included during the study period of 2012-2014. Twenty-one patients were treated with PEG-IFNα plus entecavir (combination arm) and 19 with PEG-IFNα alone (monotherapy arm). The mean age of the patients was 26.7 ± 6.8 years, 31 were male and 14 were HBeAg reactive; 7 in each arm.

Demographic and baseline clinical characteristics of the patients are shown in Table 1. Age, gender, body mass index, degree of fibrosis and inflammation on liver biopsy, ALT, HBeAg status, and HDV RNA levels were comparable to the combination and monotherapy arm patients. However, platelet count in monotherapy arm was lower than in the combination arm. Baseline HBsAg and HBV DNA levels were correlated (Pearson correlation = 0.625, *P* < 0.001). Liver biopsy was available in all cases as one of the inclusion criteria. Mild inflammation was seen in 6 and moderate to severe in 34 patients. Stage of the disease was 0-2 in 18 and 3-4 in 22 patients. Cirrhosis of the liver as evident from histology, ultrasound or clinical examination was present in 8 (20%) patients.

Two log reduction in HDV RNA levels at 24 wk of therapy was achieved in 9 (43%) patients receiving combination therapy and in 12 (63%) patients receiving PEG-IFNα alone (*P* = 0.199) (Figure 1). There was no significant difference in the HBsAg log10 levels after six months of therapy; 4.13 ± 0.91 in the combination arm *vs* 4.01 ± 0.51 in the monotherapy arm (*P* = 0.608), and a mean decline in HBsAg levels (*P* = 0.579). At the end of treatment, HDV RNA was negative in 8 patients (38%) receiving combination therapy and in 10 patients (53%) receiving PEG-IFNα-2a alone by intention to treat analysis (*P* = 0.356). ALT normalization was seen in 4 (19%) patients of the combination arm and 7 (37%) patients of the monotherapy arm (*P* = 0.293). One 29-year-old male patient in the combination arm

Table 2 Factors associated with hepatitis D virus RNA negativity at 24 wk post-treatment *n* (%)

Variable	Responders (*n* = 15)	Non-responders (*n* = 25)	*P* value
Age (mean, yr)	27.9 ± 8.4	25.9 ± 5.7	0.654
Gender (male:female)	12:3	19:6	1.00
Body mass index (kg/m^2)	23.8 ± 4.2	21.9 ± 3.8	0.158
ALT (mean IU/L)	103 ± 44	80 ± 50	0.033[1]
GGT (mean IU/L)	45 ± 21	66 ± 72	0.700
Inflammatory activity on biopsy			0.493
0-1	3 (20)	3 (12)	
2-3	12 (80)	22 (88)	
Fibrosis on biopsy			0.412
0-2	8 (53)	10 (40)	
3-4	7 (47)	15 (60)	
Cirrhosis	2 (13)	6 (24)	0.686
HBeAg reactive	4 (27)	10 (40)	0.502
Baseline HDV RNA	7.01 ± 1.25	4.61 ± 1.91	0.072
Baseline HBsAg	4.38 ± 0.63	4.32 ± 0.53	0.727
Treatment arm			0.567
PEG-IFNα + entecavir (*n* = 21)	7 (33)	14 (67)	
PEG-IFNα alone (*n* = 19)	8 (42)	11 (58)	
Two log of HDV RNA reduction at week 24	15 (100)	6 (24)	< 0.001[1]
Baseline HBeAg reactive	4 (27)	10 (40)	0.502
24 wk HBsAg level	3.97 ± 1.01	4.31 ± 0.45	0.476
One log reduction of HBsAg level at 24 wk	5 (33)	4 (16)	0.255
Patients with decrease in HBsAg level at 24 wk from baseline	12 (80)	12 (48)	0.056
HBeAg reactive patients (*n* = 14) who seroconverted	4/4 (100)	2/10 (20)	0.015[1]

[1]Significant *P* value. ALT: Alanine aminotransferase; GGT: Gamma glutamyl transferase; HBeAg: Hepatitis B e antigen; HDV: Hepatitis D virus; PEG-IFNα: Pegylated interferon alfa; HBsAg: Hepatitis B surface antigen.

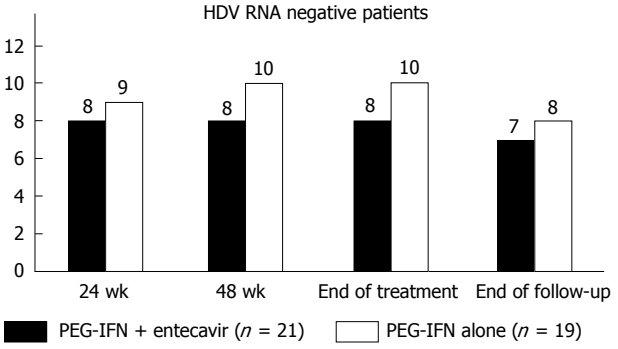

Figure 2 Number of patients who became hepatitis D virus RNA negative. HDV: Hepatitis D virus; PEG-IFN: Pegylated interferon.

lost HBsAg and became anti-HBs antibody positive. His baseline parameters were HBsAg 2903 IU/mL (log10 = 3.46), HBeAg negative with undetectable HBV DNA, and HDV RNA 158000 IU/ml (log10 = 5.20). At 24 wk of treatment, his HBsAg level was 11.6 IU/mL, and HDV RNA negative. HBsAg became undetectable at 48 wk and he developed anti-HBs antibodies.

Two patients in the monotherapy arm relapsed during the 24 wk post-treatment period and one patient in the combination arm was lost to follow-up, decreasing the persistent virological clearance 24 wk post treatment to 7 (33%) in the combination arm and 8 (42%) in the monotherapy arm (P = 0.567) (Table 2 and Figure 2) in an intention to treat analysis. End of follow-up biochemical response was seen in only patients with the virologic response; 5/21 (24%) and 7/19 (37%) patients of combination arm and monotherapy arm respectively (P = 0.369).

Though there were no statistical differences in log reduction of HBsAg levels at 24 wk of treatment between responders and non responders, there was a trend of decrease in HBsAg levels (P = 0.056). Out of 14 HBeAg reactive patients, HBeAg seroconversion was seen in 2 patients on combination arm and 4 patients of monotherapy arm. Both patients of the combination arm and 2 patients of the monotherapy arm achieved persistence HDV RNA clearance during the follow-up period while one patient relapsed and another had virological breakthrough during treatment. In contrast, 7 out of 8 patients, who did not seroconvert, were null responders and one patient could not complete treatment due to complications of treatment (combination arm).

One patient from the combination arm could achieve only one log reduction in the HDV RNA levels at 24 wk of treatment, and was considered as a non-responder according to the protocol. He was taken off the study and was considered a treatment failure in an intention to treat analysis. However, he continued to receive PEG-IFNα monotherapy for another 24 wk and became HDV RNA negative at the end of treatment and the response persisted 24 wk post treatment.

The side effects reported by these patients were usually of PEG-IFN and included nausea, weakness, fever, decreased appetite, bloating, body aches, headaches, weight loss. These side effects did not require a dose reduction. One patient developed transient

neutropenia and responded to subcutaneous filgrastim. Two patients discontinued treatment; one in each arm during the treatment before 24 wk of therapy. One patient in the monotherapy arm developed ascites while treatment was stopped in another patient in the combination arm due to severe depression.

DISCUSSION

We used PEG-IFNα in combination with entecavir to treat HDV patients for the first time. The results of our study are in congruence with the previous studies that the combination treatment of nucleos(t)ides with PEG-IFNα does not have any edge over PEG-IFN monotherapy in terms of sustained clearance of HDV RNA[10].

Some of the previous studies, including one of ours, have shown that response to the treatment can be predicted by the HDV RNA assessment at six months, and may give a clue whether to stop treatment[11,12]. Patients with negative HDV RNA at six months are more likely to have sustained virologic response[5] while non-responders could be identified by a less than 3 log decrease of HDV RNA at 6 mo of treatment[11]. We used two log reduction at 24 wk as a criterion to continue treatment in our protocol. One of our patients from the combination arm had one log reduction at 24 wk, was taken off the study as non-responder but he continued treatment and showed persistent virological clearance. As there are not many treatment options for chronic hepatitis D, we may suggest that the patients, even with one log reduction in the viral load at 24 wk of therapy, who continue to show steady decline in HDV RNA levels may remain on treatment.

We had a low relapse rate in this study compared to our previous experience[5] as according to the protocol only better responders continued treatment, *i.e.,* patients who had a 2 log reduction in HDV RNA levels at 24 wk of treatment. Moreover, treatment was extended to 72 wk instead of stopping at 48 wk. It may be beneficial to extend treatment duration beyond 48 wk in good responders to decrease the relapse rate, *i.e.,* patients who show a reduction in HDV RNA and HBsAg levels, and HBeAg reactive patients who seroconvert during the treatment. However, proper way to judge this dictum could be a randomized trial comparing 48 wk *vs* 72-96 wk of therapy. Extending duration of therapy may also useful in patients with slow but steady decline of HDV RNA and HBsAg levels.

Heller *et al*[13] studied prolonging therapy of chronic hepatitis D with PEG-IFNα for up to 5 years. Only three of 12 patients treated achieved a complete virologic response, endpoint defined as the combination of undetectable HDV RNA with loss of HBsAg and anti-HBsAg seroconversion in serum. Thus, given the poor response rates, and long-term risks of interferon-based therapies, we have to be selective in choosing our patients for a prolonged therapy. The long term results of HIDIT-1 study[6] where patients were treated for 48 wk *vs* HIDIT-2 study[7] when the treatment was extended for 92 wk were not much different. Thus, given the poor response rates, and long-term risks of interferon-based therapies, we have to be selective in choosing our patients for a prolonged therapy and we cannot make it a rule. Optimized HBsAg titer monitoring and checking HDV RNA levels may improve the outcome[14,15].

In our study, HBeAg reactive patients who seroconverted during the treatment had a less chance of relapse. One of our responder patients in the combination arm, who had a lower HBsAg level as compared to the average of the cohort, lost HBsAg during the treatment. Interferon based therapy is known to induce HBsAg seroconversion and it is usually associated with low pretreatment HBsAg levels[16].

We did not check for genotypes of HBV and HDV for this study as it is already known that the genotype of hepatitis D is 1[17] and of hepatitis B is D in our region[18]. We followed our patients for six months post treatment. Late HDV RNA relapses may occur after PEG-IFNα therapy of hepatitis delta and thus the term "sustained virological response" should be used with caution in HDV infection[19]. There was a possibility of a higher relapse rate in our patients if we had followed up our patients for a longer period.

In conclusion, combination treatment did not show any additional benefit in terms of HDV RNA suppression and HBsAg reduction as compared to PEG-IFNα alone. Liver fibrosis and HBsAg levels did not predict HDV RNA response. HDV RNA response at 24 wk, HBeAg seroconversion and any reduction in HBsAg levels during treatment may predict the patients who are going to have a better outcome.

ACKNOWLEDGMENTS

We are thankful to Dr. Syed Salman Ali and Dr. Muhammad Mustafa for their help as coordinator in the initial phases of study.

COMMENTS

Background

Chronic hepatitis D is a difficult to treat infection. Six months post treatment response is seen only in one quarter of the patients treated with pegylated interferon alfa (PEG-IFNα).

Research frontiers

In an attempt to improve the response of PEG-IFN, the authors combined entecavir which is a reverse transcriptase inhibitor.

Innovations and breakthroughs

This is the first study to evaluate the efficacy of subcutaneous PEG-IFN with oral entecavir compared to PEG-IFN alone for the treatment of hepatitis D infection.

Applications

This study showed that the combination treatment did not have any additional benefit in terms of hepatitis D virus (HDV) RNA suppression and hepatitis B surface antigen reduction as compared to PEG-IFN alone.

Terminology

HDV is a small spherical enveloped RNA virus. It is considered to be a subviral satellite because it can propagate only in the presence of the hepatitis B virus. There is no satisfactory treatment available to treat this infection. However, PEG-IFN is often used.

Peer-review

The paper indicates in a randomized trial that the addition of entecavir to PEG-IFN does not increase efficacy *vs* PEG-IFN monotherapy in the treatment of chronic hepatitis D. The data are valuable as they extend and confirm previous anecdotal reports.

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P- Reviewer: Cunha C, Gatselis NK, Rizzetto M
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World Journal of Hepatology

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DOI: 10.4254/wjh.v8.i14.632

World J Hepatol 2016 May 18; 8(14): 632-636
ISSN 1948-5182 (online)

CASE REPORT

Direct acting antiviral therapy is curative for chronic hepatitis C/autoimmune hepatitis overlap syndrome

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Author contributions: Sahebjam F and Sigal SH designed the report; Hajdu CH performed pathologic analysis; Nortey E acquired clinical data.

Institutional review board statement: This case report was exempt from the Institutional Review Board standards at the New York University School of Medicine.

Informed consent statement: The patients involved in this case report gave verbal informed consent to be included. Written informed consent was exempt from the Institutional Review Board standards at the New York University School of Medicine.

Conflict-of-interest statement: Samuel H Sigal received research support from AbbVie and Gilead, consulting fees from AbbVie and Gilead, and was a member of the Gilead Speakers' Bureau. The other authors have no conflicts of interest to declare.

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Received: December 29, 2015
Peer-review started: January 1, 2016
First decision: February 2, 2016
Revised: February 19, 2016
Accepted: March 9, 2016
Article in press: March 14, 2016
Published online: May 18, 2016

Abstract

Autoimmune phenomena are common in patients with chronic hepatitis C. Management of chronic hepatitis C/autoimmune hepatitis syndrome has until recently been problematic due to the adverse effects of interferon on autoimmune processes and immunosuppression on viral replication. In this report we describe 3 patients with chronic hepatitis C/autoimmune hepatitis overlap syndrome who responded rapidly to direct acting antiviral therapy. The resolution of the autoimmune process supports a direct viral role in its pathophysiology.

Key words: Hepatitis C; Autoimmune hepatitis; Overlap syndrome; Direct acting antiviral therapy

Core tip: Autoimmune phenomena are common in patients with chronic hepatitis C, and occasionally patients with chronic hepatitis C have concomitant features of autoimmune hepatitis (AIH). Management of these patients has until recently been problematic due to the adverse effects of interferon on autoimmune processes and immunosuppression on viral replication. In this report we describe 3 patients with chronic hepatitis C/AIH overlap syndrome who responded rapidly to direct acting anti-viral therapy with prompt normalization of liver tests and progressive decrease in the serologic

markers of AIH. The resolution of the autoimmune process supports a direct viral role in its pathophysiology.

Sahebjam F, Hajdu CH, Nortey E, Sigal SH. Direct acting antiviral therapy is curative for chronic hepatitis C/autoimmune hepatitis overlap syndrome. *World J Hepatol* 2016; 8(14): 632-636 Available from: URL: http://www.wjgnet.com/1948-5182/full/v8/i14/632.htm DOI: http://dx.doi.org/10.4254/wjh.v8.i14.632

INTRODUCTION

Chronic hepatitis C virus (HCV) infection has a worldwide prevalence of 2%-3% and is a leading cause of cirrhosis and hepatocellular carcinoma in Western countries[1]. In 40%-74% of patients, HCV is associated with autoimmune phenomena ranging from positive serologic markers to wide spread autoimmune diseases, including rheumatoid arthritis, mixed cryoglobulinemia, B-cell lymphoma, systemic lupus erythematosus, sicca syndrome, autoimmune thyroiditis, and autoimmune hepatitis (AIH).

AIH is a condition of unknown etiology characterized by a progressive inflammatory process with histopathologic changes that include interface hepatitis with a predominant lymphoplasmacytic infiltrate, elevated transaminases and immunoglobulin levels, and the presence of autoantibodies. To standardize diagnostic criteria, the International Autoimmune Hepatitis Group (IAHG) devised a scoring system to categorize patients as definite AIH, probable AIH and not AIH[2] in which points are distributed based on the presence of antinuclear antibody (ANA), anti smooth antibody (ASMA or F-Actin Antibody), anti-soluble liver/liver pancreas antigen, immunoglobulin G (IgG) level, liver histology and the absence of viral hepatitis.

In patients with chronic hepatitis C, markers of AIH are frequently present. Up to 40% of HCV patients may have positive ANA, SMA, and LKM-1 autoantibodies[3]. In most cases, titers are usually low, and cases with positive serologies are in general histologically indistinguishable from those without detectable antibodies. However, patients with an autoimmune overlap syndrome in whom liver biopsies reveal features of both chronic hepatitis C and inflammatory features characteristic of AIH are occasionally encountered[4].

The treatment of patients with HCV/AIH overlap syndrome has until recently been challenging. Because interferon (IFN) therapy for chronic HCV can trigger latent AIH and lead to severe hepatic failure, there are significant concerns about its use in patients with preexisting autoimmune processes[5]. Immunosuppression, on the hand, has an adverse effect on viral replication[6]. In this report, we present three patients with AIH/hepatitis C overlap syndrome in whom both processes rapidly responded to interferon-free antiviral therapy.

CASE REPORT

Case report 1

A 22-year-old Caucasian man with chronic hepatitis C presented with mild generalized fatigue and anhedonia. Risk factors for infection included intravenous drug use and possible vertical transmission. Physical examination did not reveal stigmata of advanced liver disease. Initial laboratory evaluation was remarkable for markedly elevated aspartate aminotransferase (AST) 314 U/L (normal, 15-46) and alanine aminotransferase (ALT) 608 U/L (normal, 15-65) levels, total bilirubin 0.6 mg/dL (normal, 0-1), albumin 4.5 g/dL (normal, 3.5-5), international normalized ratio 1.1, platelet count of 156 K/uL (normal 150-400), HCV RNA viral load of 1410000 IU/mL (6.15 logs), HCV genotype 1. Serological markers of AIH were remarkable for elevated IgG at 2100 mg/dL (normal, 700-1600), positive ANA (1:80), and positive F-actin antibody of 37 units (normal, 0-19).

Liver biopsy showed established cirrhosis with mild to moderate activity. Inflammatory infiltrates composed of lymphocytes with lymphoid aggregate formation, polymorphonuclear cells and scattered plasma cells were present in the portal tracts, interface and fibrous septae. A brisk lobular lymphoplasmacytic infiltrate with rare acidophil bodies was also present. Due to the severity of the inflammatory activity, the overall histologic appearance was suggestive of an autoimmune process with a simplified IAHG, diagnostic score of 6 (probable AIH).

The patient was treated with budesonide 3 mg three times daily for two months with limited biochemical response (ALT, 343 U/L) and response in either the total protein level (8.2 g/dL, pre-; 7.6 g/dL, post-) or HCV viral load [1523252 IU/ML (6.18 logs)]. Budesonide was then discontinued, and a 12 wk interferon-free regimen of simeprevir and sofosbuvir started with prompt normalization of aminotransferase levels, normalization of the IgG level (1350 mg/dL), and achievement of a sustained response. F-Actin antibody titer did not change following treatment (37 U before, 36 U after) (Figure 1).

Case report 2

A 62-year-old man with chronic hepatitis C presented with generalized fatigue. Risk factors for hepatitis C infection included a blood transfusion at birth. Past medical history was significant for epilepsy and depression. Physical examination did not reveal stigmata of chronic liver disease. Laboratory evaluation was remarkable for AST 447 U/L, ALT 480 U/L, total bilirubin of 0.8 mg/dL, albumin 3.9 g/dL, international normalized ratio 1.4, HCV genotype 1, platelet count of 115 K/uL, HCV RNA viral load 1660000 IU/mL. Serologic markers of AIH were remarkable for elevated IgG at 3030 mg/dL, ANA titer 1:80, and F-actin antibody titer of 24 U.

Liver biopsy revealed mild to moderate portal infiltration consisting of lymphocytes with lymphoid aggregate formation, plasma cells and eosinophils. Interface

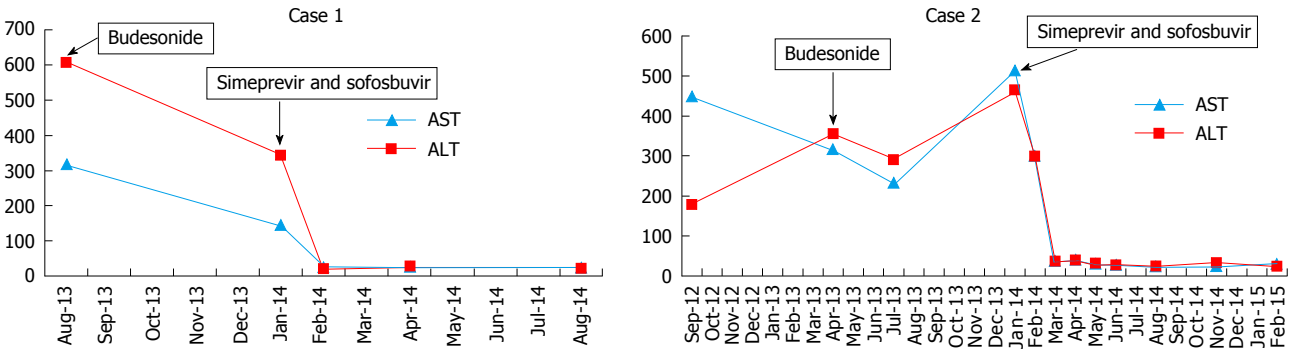

Figure 1 Aspartate aminotransferase and alanine aminotransferase levels in case 1 and case 2 prior and after immunosuppression and hepatitis C infection treatment. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

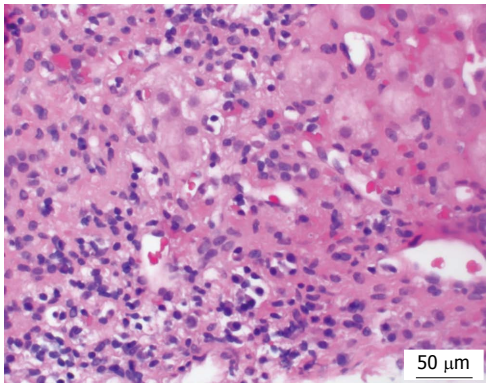

Figure 2 Liver biopsy of case 3 demonstrating interface activity with abundant plasma cell infiltration (600 × H and E staining).

activity was moderate with plasma cells easily identified and lobular inflammation was mild to moderate with acidophil bodies readily found. Macrovesicular steatosis in 30% to 40% of the specimen with focal ballooning degeneration and focal bridging fibrosis (stage 3) was also present. The moderate interface activity with numerous plasma cells was consistent with an autoimmune process with a simplified IAHG diagnostic score of 6 (probable AIH)[7].

The patient declined interferon therapy and was started on budesonide 3 mg twice daily without significant effect on ALT or IgG levels (Figure 1) and HCV viral load remain unchanged (1177912 IU/mL). After 6 mo, budesonide was tapered to 3 mg daily, and a repeat liver biopsy was performed which revealed persistent portal and lobular inflammation, worsening ballooning degeneration and progression to cirrhosis. Budesonide was discontinued, and interferon-free therapy with 12 wk of simeprevir and sofosbuvir initiated. Aminotransferase levels promptly normalized. HCV RNA was undetectable by treatment week 8, and a sustained virologic response was achieved. During and after completion of therapy, IgG and F-actin levels progressively decreased (2070 mg/dL, 15 units respectively), and ANA titer was negative one year after completion of antiviral therapy.

Case report 3

A 62-year-old African American woman with a history of alcoholism was referred for treatment of chronic hepatitis C. Risk factors included a history of intravenous drug abuse. Liver biopsy 3 years previously revealed stage Ⅳ fibrosis and moderate necroinflammatory activity with plasma cell component (Figure 2). Physical examination was significant for an enlarged left lobe of liver. Initial laboratory evaluation was remarkable for mildly elevated AST 68 U/L, ALT of 84 U/L levels, total bilirubin 0.8 mg/dL, albumin 3.6 g/dL, total protein 8.89 g/dL, international normalized ratio 1.2, platelet count of 85 K/uL, HCV RNA viral load of 285000 IU/mL (5.46 logs), HCV genotype 1a. Serological markers of AIH were remarkable for elevated IgG 3250 mg/dL, positive ANA, F-actin antibody titer of 37.

The patient was started on ledipasvir/sofosbuvir. Viral load became undetectable within 4 wk, and she achieved SVR with 12 wk of treatment. At the end of therapy, aminotransferase levels were normal (AST, 36; ALT, 27). ANA became negative, serum total protein decreased to normal level of 7.6 g/dL (normal, 6.3-8.2), and serum IgG decreased to 2300 mg/dL (normal, 700-1600). F-actin antibody titer also decreased to the normal range (17 U).

DISCUSSION

In this report, we present the response of HCV/AIH overlap syndrome to direct acting antiviral (DAA) therapy. The diagnosis of overlap syndrome was established by the presence of active viremia and characteristic biochemical, serologic, and histopathologic features of AIH. Although only a simplified AIH score of 6 was present, it is important to note that only a maximum score of 6 is possible if viral hepatitis component is not included. There were no biochemical or immunologic responses, but rather worsening pathologic changes in the one case in which a repeat liver biopsy was performed. In contrast, there was a prompt normalization of liver biochemistries and resolution of serologic features of AIH in response to DAA therapy in all three cases.

Although the pathogenesis of AIH is incompletely understood, a frequently cited mechanism is a reaction to viral infections in genetically susceptible persons. Cross-reaction between viral particles and liver auto-

antigens has been proposed as a trigger mechanism of virus induced AIH. Activation of resting T cells by inducing the release of a variety of cytokines, and polyclonal activation of lymphocytes has also been proposed to play a role. An association with measles virus was first proposed in 1987 after identification of persistent measles virus genome in lymphocytes and high antibody titers in 12 of 18 patients with AIH[8]. Vento *et al*[9] reported the development of AIH in healthy relatives of patients with AIH that was associated with cases of infectious mononucleosis due to Epstein-Barr virus (EBV) infection. In these cases, the development and persistence of autoantibodies to the asialoglycoprotein receptor were documented, and it was proposed that cross reactivity between asialoglycoprotein and EBV antibodies caused an autoimmune reaction. Recently, high prevalence of hepatitis E antibody positivity was found in patients with AIH, compared to healthy, and individuals with HCV or HBV infection[10]. Other viral infections that have been associated with AIH include hepatitis B, varicella-zoster and rubella[11].

There are several proposed mechanisms in the pathogenesis of autoimmunity in HCV. HCV facilitates lymphotropism in which clonal B-lymphocyte expansion leads to widespread autoantibody production. The HCV envelope protein E2 is able to bind to the CD81 molecule expressed on hepatocytes and B-lymphocytes, resulting in a dysregulation of cytokines with an enhanced Th1 immune response. This may cause self-reactive lymphocytes to induce autoimmunity in the chronic HCV patient. Recently, cross-reactivity between CYP2E1 and specific sequences in HCV-NS5b protein has been shown responsible for the production of auto-antibodies targeting self-proteins[12].

There are no established treatment strategies for HCV/AIH overlap syndrome. IFN alone previously was avoided due to the concern about its potential to induce an autoimmune flare. Early reports of steroid therapy prior to the era in which HCV RNA testing was available frequently included RNA negative patients, making determination of efficacy difficult to assess. Several small series and case reports have advocated pre-treatment with corticosteroids with or without azathioprine followed by IFN-based therapy to prevent an IFN-induced flare[13-15].

The development of interferon-free direct acting antiviral regimens has revolutionized the treatment of HCV. These new treatments are potent, safe, and achieve rapid normalization of aminotransferase levels and viral suppression within the first few weeks of therapy. This is the first description of DAA therapy for HCV/AIH overlap syndrome. The rapid normalization of aminotransferase level and suppression of viral RNA followed by a gradual disappearance of autoimmune markers without immunosuppression supports the hypothesis that the viral infection triggers the autoimmune response. Based on our cases, we propose DAA agents as an initial treatment for patients with HCV/AIH overlap syndrome and early reassessment of response. Corticosteroids and immunosuppression should be reserved for those who are refractory to this approach.

COMMENTS

Case characteristics

Three patients presented for treatment of chronic hepatitis C.

Clinical diagnosis

Severe hepatitis with markedly elevated aminotransferase levels.

Differential diagnosis

Chronic hepatitis C with severe activity or superimposed second process such as autoimmune hepatitis (AIH).

Laboratory diagnosis

Positive anti-nuclear antibody and anti-smooth muscle antibody, elevated immunoglobulin G (IgG) level.

Pathologic diagnosis

Liver biopsy reveal in all three cases prominent numbers of plasma cells compatible with AIH.

Treatment

Treatment with steroids in the form of budesonide was not effective. However, there was prompt resolution of both the chronic hepatitis C and AIH with direct acting anti-viral therapy.

Related reports

Reports have suggested an infectious precipitant for AIH. Previous therapeutic approach for the treatment of chronic hepatitis C/AIH have usually involved steroid therapy followed by interferon-based therapy with variable success.

Term explanation

In chronic hepatitis C/AIH overlap syndrome, hepatitis C viremia is present in patients with AIH as defined by the presence of anti-nuclear and anti-smooth muscle antibodies, elevated IgG levels, and lymphoplasmacytic infiltrates on liver biopsy.

Experiences and lessons

Resolution of both the viral and AIH in response to direct acting antiviral therapy supports the hypothesis that the autoimmune process is caused by the viral infection.

Peer-review

In the present manuscript, the authors described 3 case patients with chronic HCV/AIH syndrome who were treated with direct acting antiviral (DAA). DAA treatment promptly induced the normalization of liver biochemistries and the resolution of serological features of AIH. The present report is potentially easily understandable and very interesting.

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P- Reviewer: Ito H, Lau WY, Morales-Gonzalez J
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