ISSN 1948-5182 (online)

World Journal of *Hepatology*

World J Hepatol 2014 May 27; 6(5): 263-362

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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WJH

World Journal of Hepatology

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Monthly Volume 6 Number 5 May 27, 2014

AIM AND SCOPE

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INDEXING/ ABSTRACTING

World Journal of Hepatology is now indexed in PubMed Central, PubMed, Digital Object Identifier, Directory of Open Access Journals, and Scopus.

NAME OF JOURNAL
World Journal of Hepatology

ISSN
ISSN 1948-5182 (online)

LAUNCH DATE
October 31, 2009

FREQUENCY
Monthly

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

PUBLICATION DATE
May 27, 2014

World Journal of Hepatology

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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4254/wjh.v6.i5.263

World J Hepatol 2014 May 27; 6(5): 263-273
ISSN 1948-5182 (online)

REVIEW

Obesity and non-alcoholic fatty liver disease: Disparate associations among Asian populations

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Author contributions: Wong RJ and Ahmed A contributed to the study concept and design; Wong RJ contributed to the systematic review, data collection and drafting of the manuscript; Ahmed A contributed to the critical review of the manuscript; Wong RJ and Ahmed A contributed to the revision and finalization of the manuscript.

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Received: October 25, 2013 Revised: January 15, 2014
Accepted: April 25, 2014
Published online: May 27, 2014

Abstract

Obesity is a global epidemic contributing to an increasing prevalence of obesity-related systemic disorders, including nonalcoholic fatty liver disease. The rising prevalence of nonalcoholic steatohepatitis (NASH) will in the near future lead to end-stage liver disease in a large cohort of patients with NASH-related cirrhosis and NASH is predicted to be a leading indication for liver transplantation in the coming decade. However, the prevalence of obesity and the progression of hepatic histological damage associated with NASH exhibit significant ethnic disparities. Despite a significantly lower body mass index and lower rates of obesity compared to other ethnic groups, Asians continue to demonstrate a significant prevalence of hypertension, diabetes, metabolic syndrome and NASH. Ethnic disparities in central adiposity and visceral fat distribution have been hypothesized to contribute to these ethnic disparities. The current review focuses on the epidemiology of obesity and NASH among Asian populations.

Key words: Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Obesity; Metabolic syndrome; Asians; Hepatocellular carcinoma

Core tip: Non-alcoholic fatty liver disease (NAFLD) is rapidly becoming a major contributor of chronic liver disease worldwide. The increasing prevalence of NAFLD among Asians reflects both an increasing awareness and diagnosis and the increasing risk of obesity and obesity-related diseases among this population. Ethnic disparities in the impact of weight gain on the development of obesity-related diseases is especially important for Asian populations, who have greater rates of central obesity and visceral deposition of fat and therefore are at greater risk of obesity-related diseases, such as NAFLD, at a lower body mass index.

Wong RJ, Ahmed A. Obesity and non-alcoholic fatty liver disease: Disparate associations among Asian populations. *World J Hepatol* 2014; 6(5): 263-273 Available from: URL: http://www.wjgnet.com/1948-5182/full/v6/i5/263.htm DOI: http://dx.doi.org/10.4254/wjh.v6.i5.263

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) spans a spectrum of liver diseases that ranges from simple steatosis of the liver to progressive inflammation and fibrosis, resulting in non-alcoholic steatosis (NASH) and cirrhosis[1]. While the definition of NAFLD relies heavily on the clinical exclusion of significant alcoholic liver disease as well as other concomitant chronic liver diseases that can mimic similar histopathological features, one of the major hallmark features of NAFLD is the consistent association with type 2 diabetes mellitus, hypertension, hyperlipidemia and obesity[1-5]. The rising epidemic of obesity and obesity-related diseases in many post-industrialized countries has been accompanied by a concurrent rise in

the prevalence of NAFLD. These emerging trends along with our better understanding of the pathophysiology of NAFLD clearly highlight the important role of obesity and obesity-related diseases in the increasing prevalence of NAFLD.

Several studies have reported the alarming increase in obesity and metabolic syndrome in western countries[6-12]. One recent large population-based study in the United States, utilizing data from the National Health and Nutrition Examination Surveys from 2009-2010 (NHANES), reported obesity rates of 35.5% among men and 35.8% among women[7]. Furthermore, population based studies utilizing United States census based data have demonstrated a concurrent rise in the prevalence of obesity-related diseases, such as hypertension and diabetes mellitus[13-18]. Among the same population, several studies have reported an increasing prevalence of NAFLD, suggesting that the rising rates of NAFLD are a consequence of the rising rates of obesity and metabolic syndrome in these populations. In fact, a recent study by Charlton *et al*[19] estimates that the rising prevalence of NAFLD in the United States population will soon lead to large cohorts of patients with decompensated cirrhosis from NASH and that NASH will soon become the leading indication for liver transplantation in the United States.

However, the epidemiology of obesity and obesity-related diseases demonstrates significant ethnic disparities. For example, several studies among both western and eastern cohorts demonstrate that Asians as a group consistently have a much lower body mass index (BMI) compared to other ethnic groups[20-23]. The relatively lower BMI is not protective in Asians. The rates of hypertension and diabetes mellitus, while somewhat lower, still continue to demonstrate rising trends among Asians[20]. In addition, cohort studies have demonstrated that despite having significantly lower BMI than other ethnic groups, Asians have a surprisingly high prevalence of NAFLD[24]. While not entirely elucidated, one emerging theory for this discrepancy between BMI and NAFLD prevalence may result from ethnic differences in the distribution of body fat, with more central adiposity and visceral fat deposition reported among individuals of Asian ethnicity[25-29]. Nevertheless, the increasing prevalence of obesity, metabolic syndrome and NAFLD among the Asian population will contribute to a large burden of chronic disease. The current paper reviews the concerning rise in obesity and NAFLD, with a focus on Asian populations.

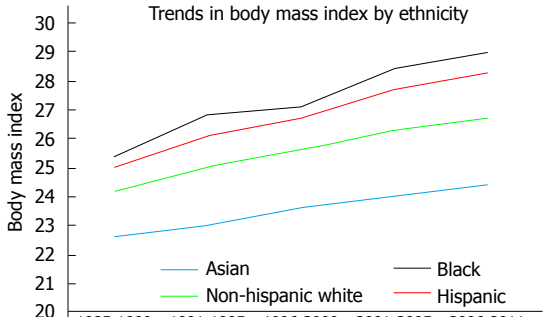
OBESITY DISPARITIES

The global obesity epidemic has been associated with the increasing burden of obesity-related diseases such as coronary artery diseases, hypertension and diabetes mellitus[9-12]. In addition, a link has been established between obesity and NAFLD such that obesity increases the risk of progression of hepatic inflammation and fibrosis leading to NASH-related cirrhosis. However, one emerging theme in the study of obesity is the ethnic disparities in the prevalence of obesity as well as the impact of weight gain on the overall risk of obesity-related diseases.

Several studies have reported ethnic disparities in the prevalence of obesity, with higher obesity rates in minority groups such as blacks and Hispanics[20,30-34]. However, Asians as a group generally have a lower BMI and lower prevalence of obesity compared to other ethnic groups[20-23]. Despite lower obesity prevalence, higher rates of metabolic syndrome have been reported in Asians compared to other ethnic groups at similar BMI levels[20]. These findings demonstrate that BMI thresholds for defining overweight and obesity should not be applied uniformly to all ethnic cohorts.

Current BMI categories set forth by the United States Centers for Disease Control and Prevention (BMI > 25 kg/m^2 as overweight and BMI > 30 kg/m^2 as obese) were intended to predict an individual's risk of developing diseases associated with overweight and obese categories[35]. Two large population-based longitudinal studies, the San Antonio Heart Study and the Insulin Resistance Atherosclerosis Study, demonstrated a strong association of BMI with the risk of metabolic syndrome. Obese individuals (BMI > 30 kg/m^2) were three to eight times more likely to develop metabolic syndrome compared to individuals with BMI < 25 kg/m^2[31,36]. In addition, the association of obesity and metabolic syndrome with development of complications such as cardiovascular disease and diabetes mellitus is well established[37-40]. However, similar to ethnic disparities in the prevalence of obesity, the correlation of BMI with obesity-related diseases is not uniform across all ethnicities. For example, using data from NHANES, Palaniappan *et al*[30] demonstrated that fasting insulin levels, a marker of insulin sensitivity and risk of diabetes, was 19%-26% higher in blacks and 17-22% higher in Hispanics when compared to non-Hispanic whites with similar BMI. This disparity was also noted among Asians, with one study demonstrating significantly higher rates of metabolic syndrome in Asians compared to other ethnic groups with similar BMI. For example, Palaniappan *et al*[20] demonstrated that the predicted prevalence of metabolic syndrome in non-Hispanic white women aged 55 years with BMI 25 kg/m^2 was 12% compared to 30% in Asians with similar demographics and BMI. Furthermore, compared to white men with BMI 25 kg/m^2, comparable prevalence of metabolic syndrome was seen in Asian men with BMI 19.9 kg/m^2.

Using data from the California Department of Public Health and the United States Centers for Disease Control and Prevention, our group performed an in-depth analysis of ethnic disparities in obesity and obesity-related diseases with a focus on Asian populations. From 1985 to 2011, Asians as a group had the lowest BMI and lowest obesity prevalence (Asians: 22.6 ± 3.3 kg/m^2 in 1985-1990 to 24.4 ± 4.3 kg/m^2 in 2006-2011; non-Hispanic whites: 24.2 ± 4.1 kg/m^2 in 1985-1990 to 26.7 ± 5.5 kg/m^2 in 2006-2011; blacks: 25.4 ± 4.5 kg/m^2 in 1985-1990 to 29.0



	1985-1990	1991-1995	1996-2000	2001-2005	2006-2011
Asian	22.6	23.0	23.6	24.0	24.4
Non-hispanic white	24.2	25.0	25.6	26.3	26.7
Black	25.4	26.8	27.1	28.4	29.0
Hispanic	25.0	26.1	26.7	27.7	28.3

Figure 1 Trends in body mass index over time stratified by ethnicity, 1985-2011, California behavioral risk factor survey database.

± 6.9 kg/m^2 in 2006-2011; Hispanics: 25.0 ± 4.1 kg/m^2 in 1985-1990 to 28.3 ± 5.8 kg/m^2 in 2006-2011) (Figure 1). Despite lower overall BMI, Asians had comparable or even higher rates of hypertension and diabetes mellitus compared to other ethnic groups. To evaluate whether weight gain as measured by BMI affected ethnic groups similarly, we created a multivariate logistic regression model to assess the effect of each one unit increase in BMI on the risk of hypertension or diabetes mellitus (Table 1). In our cohort model, each one unit increase in BMI was associated with 15% increased risk of hypertension in Asians, compared with 11% increase among non-Hispanic whites and 8% increase among blacks and Hispanics. When evaluating the impact of weight gain on the risk of diabetes mellitus, each one unit BMI was associated with 15% increased risk of diabetes mellitus among Asians, compared to 11% increase among non-Hispanic whites, 7% increase among blacks and 8% increase among Hispanics. These data suggest that despite having lower BMI, weight gain as measured by BMI disproportionately affects Asians to a greater degree. Furthermore, similar risks of hypertension and diabetes mellitus among non-Hispanic whites and blacks were seen in Asians at significantly lower BMI. For example, risks of hypertension among Asians with BMI > 22 kg/m^2 were similar to non-Hispanic whites with BMI > 27 kg/m^2 and blacks with BMI > 28 kg/m^2 (Figure 2). While many theories have been proposed to explain these disparities, ethnic differences in body fat distribution may be a major contributing factor. Previous studies evaluating the correlation of BMI with percentage body fat demonstrated that blacks generally have more lean mass and less fat mass compared to whites. In contrast, Asians have more central adiposity and visceral fat distribution, which carries a greater risk of developing cardiovascular and metabolic diseases[25-29].

Acknowledging these disparities, several studies have suggested that current thresholds for defining obesity and overweight in Asians may not accurately reflect the risk of developing obesity-related diseases and BMI thresholds should be lowered for Asian cohorts[41,42]. In 2000, the World Health Organization Western Pacific Regional Office proposed a lower cutoff of BMI > 25 kg/m^2 for obesity in Asian populations[43]. Several Asian countries have begun to adopt this modified BMI categorization[44-46]. Additional studies have attempted to incorporate additional anthropometric tools to better stratify the risk of metabolic diseases among Asians. Using a cross sectional population-based survey study of 2947 patients in China, Shao *et al*[47] demonstrated that waist-height ratio was significantly better at predicting risk of metabolic syndrome than BMI or waist circumference alone. Liu *et al*[48] performed a similar evaluation among a cross sectional cohort of 772 Chinese patients. BMI, waist circumference and waist-hip ratio were found to have similar predictive power for risk of metabolic diseases, such as hypertension, diabetes mellitus and dyslipidemia. While solely relying on BMI to predict risk of obesity-related diseases such as NAFLD has several limitations, these additional complementary anthropometric tools may improve risk stratification.

DISPARATE ASSOCIATION OF NAFLD AND BMI

While studies in western populations clearly indicate that NASH will be a leading cause of chronic liver disease, less is known about the epidemiology of NAFLD among Asian populations. Recent community-based studies from Asian countries, including Japan, China, Taiwan, and Korea, indicate that the overall NAFLD prevalence reaches as high as 45% with year-specific analyses, demonstrating a continued rise in NAFLD prevalence with time[49-55]. Additional studies from the Asia-Pacific region demonstrated similar trends of NAFLD prevalence in India, Malaysia, Singapore and Indonesia[56-62]. Wong *et al*[63] performed a large cross-sectional study in Hong Kong to assess the community prevalence of NAFLD using proton nuclear magnetic resonance (p-NMR) spectroscopy. A total of 922 patients randomly selected from the Hong Kong census database without chronic liver disease completed a full clinical assessment. Among this cohort, p-NMR was utilized to measure intrahepatic triglyceride content with a cutoff of 5% used to distinguish patients with and without fatty liver disease. Transient elastography was also utilized to assess for hepatic fibrosis with a cutoff of 9.6 kPa to define advanced fibrosis. Overall, the cohort was 42.2% men and average BMI was 22.8 ± 3.5 kg/m^2. A total of 264 patients (26.8%) met the cutoff for diagnosis of fatty liver disease. Average BMI among the fatty liver disease cohort was 25.3 ± 3.4 kg/m^2 and among the non-fatty liver disease cohort was 21.8 ± 3.0 kg/m^2. Prevalence of advanced fibrosis was 3.7% (n = 8) and 1.3% (n = 7) among fatty liver and non-fatty liver cohorts, respectively. A similar study was performed in Shanghai that included 3175 adults that assessed for prevalence of metabolic syndrome using criteria from the National Cholesterol Education Program - Adult Treatment Panel Ⅲ and for fatty liver with ultrasonography[64]. Overall, 22.9% and 20.8% of individuals had metabolic

Table 1 Increased odds of hypertension and diabetes associated with one unit increase in body mass index

	Hypertension			Diabetes		
	OR	95%CI	*P* value	OR	95%CI	*P* value
Asian	1.15	1.13-1.18	< 0.001	1.15	1.13-1.18	< 0.001
Non-Hispanic White	1.11	1.10-1.11	< 0.001	1.11	1.11-1.12	< 0.001
Black	1.08	1.07-1.10	< 0.001	1.07	1.06-1.09	< 0.001
Hispanic	1.08	1.07-1.09	< 0.001	1.08	1.07-1.09	< 0.001

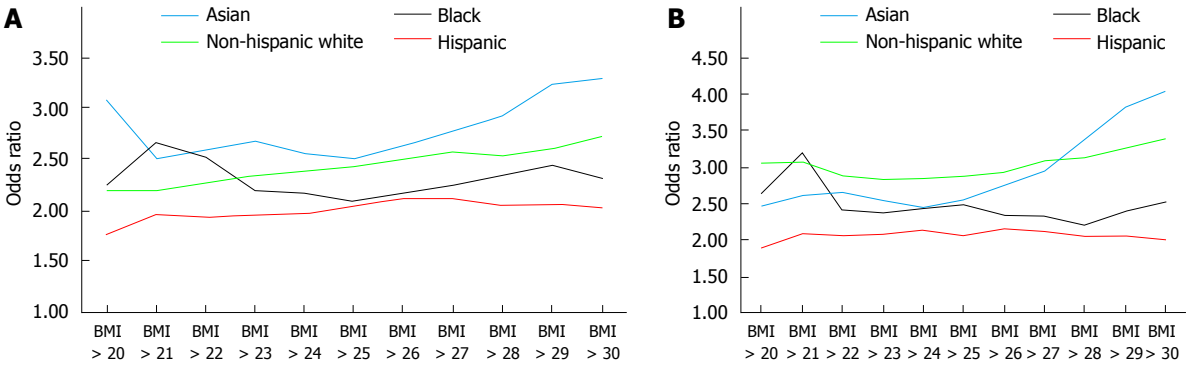


Figure 2 Odds of (A) hypertension and (B) diabetes by ethnicity and body mass index categories.

syndrome and fatty liver, respectively. The risk for fatty liver was increased among patients with abdominal obesity (waist circumference > 90 cm in men and > 80 cm in women: 32.8-fold increase), diabetes mellitus (31.6-fold increase), dyslipidemia (22.6-fold increase) and hypertension (22.3-fold). Patients that met the diagnostic threshold for metabolic syndrome had a nearly 40 times increased risk for fatty liver. When stratified by BMI, those with fatty liver disease and BMI < 25 kg/m^2 had 36.1% prevalence of metabolic syndrome. Furthermore, the presence of fatty liver disease was found to have the best positive predictive value and attributable risk percentage in detecting risk factor clustering for metabolic syndrome.

Variations in fat distribution have been implicated as one potential reason for disparate associations between BMI and NAFLD prevalence among Asian populations. It has been previously reported that the percent body fat as well as fat distribution differs significantly among Asian and non-Asian populations, such that greater central and visceral adiposity is commonly seen in Asians[25-29]. It has also been implied that as a result of this disparate distribution of fat, excessive amounts of visceral adipose tissue may occur in Asians not overweight or obese using BMI cutoffs. Greater central adiposity distribution is associated with higher risks of cardiovascular disease and metabolic syndrome[65-67]. Furthermore, ideal body weight may be different among different ethnicities and different world regions, such that while an individual does not meet BMI threshold for obesity, he may be significantly heavier than ideal body weight, and this translates into increased risk of insulin resistance and metabolic syndrome[68-70]. For example, Chang *et al*[68] performed a prospective South Korean study of 15,347 men to assess ultrasound-based diagnosis of fatty liver disease. Even among men with BMI 18.5-22.9, mild weight gains of 0.6 to 2.3 kg were associated with 38%-73% increase in the risk for fatty liver disease. This phenomena, termed "metabolically obese", namely the increased risk of insulin resistance, metabolic syndrome and NAFLD despite normal or lean BMI, has been more commonly seen in Asian populations[68-70].

Another potential theory that may partially contribute to the rising prevalence of NAFLD among Asian populations centers on the role of diet. Carbohydrates in the form of rice are a central component of the Asian diet. However, significant amounts of carbohydrates in the diet can lead to accumulation of triglycerides within the liver, which is mediated by glucose stimulated activation of the liver transcription factor, carbohydrate responsive element-binding protein (ChREBP). This process over time leads to significant hepatic steatosis and eventual progression of disease towards NASH[71-73]. However, the impact of ChREBP on hepatic steatosis among individuals with significant carbohydrate exposure may not necessarily correlate with development of insulin resistance. A recent study by Benhamed *et al*[74] evaluated ChREBP over expressing mice fed a standard diet, demonstrating that despite having increased expression of genes involved in lipogenesis/fatty acid esterification and resultant hepatic steatosis, the mice remained insulin sensitive. In addition, ChREBP over expressing mice fed a high-fat diet also showed normal insulin levels and improved insulin signaling and glucose tolerance compared with controls, despite having greater hepatic steatosis.

NATURAL HISTORY OF NAFLD IN ASIANS

The progression of inflammation and fibrosis in patients

with NAFLD is not believed to differ significantly by ethnicity. However, some earlier studies have suggested that NAFLD may be less severe with slower progression among Asian populations[75,76]. This hypothesis is complicated by several potential confounding factors. NAFLD is a relatively more recent phenomenon in Asian countries and the expected progression of disease leading to cirrhosis may occur over the next several decades. Thus, the emergence of fatty liver disease observed in the recent era in Asian populations probably lags behind western populations by several decades and the impact of large cohorts of patients with chronic liver disease and cirrhosis from NASH is expected to flood our health care system in the coming years. Another potential contributing factor is the increasing awareness and subsequent diagnosis of NAFLD among these Asian Pacific regions. Furthermore, the previously reported disparate association between BMI and metabolic syndrome that results from ethnic disparities in central adiposity and visceral fat distribution may alter the natural history of NAFLD among this population.

Despite these potential caveats, it is generally agreed that the progression of disease among patients with simple steatosis is slow compared with other diseases, such as hepatitis C virus (HCV), whereas patients with histological evidence of NASH can progress more rapidly towards advanced fibrosis and cirrhosis[1,2,77]. Long-term longitudinal studies have demonstrated increased mortality among patients with both NAFLD and NASH when compared to controls without underlying liver disease[78-86]. Interestingly, the most common cause of death among patients with NAFLD and NASH was cardiovascular diseases, reflecting the close correlations of NAFLD with metabolic syndrome and cardiovascular disease outcomes. However, simple steatosis is not always benign and progression of disease, while slow, can occur. In a single centered Hong Kong cohort, Wong *et al*[87] conducted a prospective longitudinal study of 52 patients with biopsy proven NAFLD. Among patients with simple steatosis on histology at baseline (n = 13), 15% had normal histology, 23% still had simple steatosis and 62% had evidence of histological progression towards NASH at 36 mo. While the small sample size may limit the generalization of these findings, this study raises awareness of the dynamic nature of steatosis and that simple steatosis is not necessarily benign and may warrant closer follow up.

However, progression of NAFLD to NASH-related cirrhosis is clearly associated with increased risks of hepatic decompensation and liver-related mortality[88-91]. Hui *et al*[88] performed a prospective longitudinal cohort study of 23 patients with clinically/pathologically confirmed NASH-related cirrhosis compared with 46 age and gender matched HCV-related cirrhosis patients. Over a median follow up of 60 mo (range 5-177 mo), 9/23 NASH-related cirrhosis patients developed hepatic decompensation (8 with ascites or encephalopathy, 1 with variceal bleeding). The overall survival at 1, 3, and 10 years was 95%, 90% and 84%, respectively. After multivariate regression modeling, there was no significant survival difference between the NASH-related cirrhosis and HCV-related cirrhosis cohorts. A larger United States study compared 152 patients with NASH-related cirrhosis to 150 matched patients with HCV-related cirrhosis[89]. Over 10 years of follow up, NASH patients had significantly lower mortality compared to HCV patients but this mortality difference was primarily seen in patients with Child Pugh Turcotte (CPT) class A cirrhosis. Among patients with CPT class A cirrhosis, NASH patients had significantly lower rates of hepatic decompensation, development of ascites and hepatocellular carcinoma (HCC). Similar findings were reported in a large multi-center international study of 247 patients with advanced fibrosis or cirrhosis secondary to NASH compared to 264 chronic HCV patients with similar stages of fibrosis[91]. Among the NASH cohort, there were 19.4% liver-related complications and 13.4% deaths or liver transplantation over a mean follow up of 85.6 mo. Among the HCV cohort, there were 16.7% liver-related complications and 9.4% deaths or liver transplantations over a mean follow up of 74.9 mo. After adjusting for differences in baseline characteristics, cumulative incidence of liver-related complications was significantly lower in the NASH group compared to the HCV group. However, the incidence of cardiovascular events and overall mortality was not significantly different between NASH and HCV cohorts. The results of these studies indicate that while progression of NAFLD towards NASH cirrhosis is clearly associated with increased risks of hepatic decompensation and mortality, these increased risks may not be as high as that seen among the cohort of chronic HCV cirrhosis patients.

NAFLD AND HCC

While the risks of HCC from chronic liver disease secondary to hepatitis B and HCV are better defined, the risk of HCC among patients with NASH is less well known. NASH-related HCC occurs primarily in the setting of hepatic cirrhosis[1,92-95]. A large retrospective cohort study from South Korea evaluated 329 patients with fatty liver disease associated HCC and demonstrated an increase in NAFLD-related HCC from 3.8% in 2001-2005 to 12.2% in 2006-2010[96]. A United States based study evaluated 195 NASH-cirrhosis patients from 2003-2007 with serial abdominal computed tomography and serum alpha-fetoprotein every 6 mo with a median follow up of 3.2 years[97]. Among this cohort for NASH-related cirrhosis patients, 12.8% (n = 25) developed HCC with an annual cumulative HCC incidence of 2.6%. Several additional studies, both in western and Asia-Pacific regions, report on the progression of NASH-related cirrhosis towards HCC but this rate of progression is significantly lower than that seen among patients with cirrhosis secondary to chronic HCV. Yasui *et al*[98] prospectively evaluated 412 NAFLD patients from 1990 to 2006. Among this cohort,

Table 2 Etiology of liver disease among liver transplantation recipients in the United States, 1992-2012, United Network for Organ Sharing database *n* (%)

Liver disease etiology	Pre-MELD (1992-2002)	Post-MELD (2003-2007)	Post-MELD (2008-2012)
Acute liver failure	2390 (7.9)	1639 (6.9)	1285 (5.1)
Chronic HCV	9248 (30.7)	7970 (33.5)	7803 (31.2)
Chronic HBV	1419 (4.7)	802 (3.4)	604 (2.4)
HCC	466 (1.6)	1714 (7.2)	3423 (13.7)
ALD	5027 (16.7)	3704 (15.6)	3636 (14.6)
ALD + HCV	2495 (8.3)	1845 (7.8)	1529 (6.1)
NASH	8 (0.1)	796 (3.3)	2162 (8.7)
AIH	1277 (4.2)	715 (3.0)	693 (2.8)
Cryptogenic	3460 (11.5)	2115 (8.9)	1634 (6.5)
PBC	1992 (6.6)	1009 (4.2)	795 (3.2)
PSC	1648 (5.5)	1 (4.3)	922 (3.7)
Metabolic	729 (2.4)	478 (2.0)	491 (2.0)

Metabolic includes Wilson disease, alpha-1 antitrypsin disease and hemochromatosis. MELD: Model for end stage liver disease; HCV: Hepatitis C virus; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; ALD: Alcoholic liver disease; NASH: Non-alcoholic steatohepatitis; AIH: Autoimmune hepatitis; PBC: Primary biliary cirrhosis; PSC: Primary sclerosing cholangitis.

68 patients with NASH-related cirrhosis were compared with 69 age and sex matched HCV-related cirrhosis patient controls to determine HCC risk. Overall, the 5-year cumulative HCC rate was 11.3% for NASH patients and 30.5% for HCV patients. This lower HCC risk among NASH-related cirrhosis patients compared with HCV-related cirrhosis patients was confirmed in additional studies.

While the majority of NASH-related HCC occurs in patients with cirrhosis, several studies have reported HCC development among non-cirrhotic NASH patients, with one Japanese study reporting rates of non-cirrhotic NASH-related HCC ranging from 10%-75% of cases[97-101]. The exact etiology for this non-cirrhotic pathway towards HCC is unclear. However, studies have demonstrated that obesity and diabetes mellitus, both of which are closely associated with NAFLD, are independently associated with increased risk of HCC among patients with chronic liver disease[102-104]. Furthermore, Welzel *et al*[105] utilized the National Cancer Institute's Surveillance, Epidemiology and End Results-Medicare database to evaluate the impact of metabolic syndrome on overall HCC risk among the general United States population. Among a cohort of 3649 HCC cases and 195953 comparison cohort, metabolic syndrome (as defined by National Cholesterol Education Program Adult Treatment Panel Ⅲ criteria) was associated with a significantly increased risk of HCC (OR = 2.13, 95%CI: 1.96-2.13, $P < 0.0001$).

The implications of these findings on HCC screening among NAFLD patients are a major public health issue. While more studies evaluating the long-term HCC risk among patients with NASH-related cirrhosis are needed, it is reasonable to implement standard HCC screening programs in this cohort as one would for patients with cirrhosis from other chronic liver disease etiologies. However, as with other chronic liver disease etiologies, only a fraction of NASH-related cirrhosis patients will develop HCC and the ability to better define the cohort of patients from those who will not develop HCC will be especially important in the management of this group of patients. More studies are needed to investigate risk factors for HCC development among this cohort that will allow a more targeted approach towards risk stratifications and earlier detection and treatment of HCC. However, the increasingly reported cases of HCC among non-cirrhotic NAFLD patients introduce an unexpected component to the commonly accepted pathogenesis of HCC. Clearly, these patients do not carry the same HCC risk as those patients with non-cirrhotic hepatitis B infection. However, what distinguishes those patients with non-cirrhotic NAFLD that develop HCC from those that do not? What are the important risk factors that should be incorporated into risk stratification models? How should HCC screening programs be implemented among this cohort? More studies are needed to better understand the risk factors associated with HCC development among NASH patients with and without cirrhosis.

NAFLD AND LIVER TRANSPLANTATION

The increasing prevalence of patients with NASH who develop cirrhosis and decompensated liver disease will undoubtedly lead to a major increase in the number of patients on the waiting list for liver transplantation. Several studies have already predicted that as a result of the obesity epidemic, the rising rates of NASH will become a leading indication for liver transplantation (Table 2)[19,106-108]. A recent study by Charlton *et al*[19] retrospectively evaluated liver transplantations in the United States from 2001-2009 utilizing a national liver transplantation database. This study demonstrated a significant increase in the proportion of patients undergoing liver transplantation for NASH from 1.2% in 2001 to 9.7% in 2009, making NASH the third leading indication for liver transplantation. Furthermore, the trajectory of increasing prevalence of NASH among liver transplantation recipients indicates that it will soon become the leading indication for liver transplantation. It has also been suggested that our current estimation of NASH prevalence is an underestimation, as many patients with cirrhosis secondary to cryptogenic cirrhosis may in fact be more accurately categorized as NASH. This hypothesis is supported by evidence demonstrating that cryptogenic cirrhosis patients share many similar characteristics to NASH patients, including risk factors associated with metabolic syndrome, and many patients with cryptogenic cirrhosis can in fact be more accurately categorized as NASH[109-113]. Furthermore, the outcomes associated with cryptogenic cirrhosis are also similar to those seen among patients with NASH[110-113]. Clearly, the rising prevalence of obesity and NASH patients who develop decompensated liver disease will soon become a significant cohort impacting the liver transplantation waiting list.

In Asia-Pacific regions, viral hepatitis and hepatocellular carcinoma are the leading indications for liver transplantation. Furthermore, unlike western countries, living donor liver transplantations play a more significant role in liver transplantation surgeries[114-116]. With the continued rising prevalence of NAFLD and NASH in this region, NASH may soon become a leading contributor of end stage liver disease and need for liver transplantation in the Asia-Pacific regions.

CONCLUSION

The global obesity epidemic is associated with the increasing prevalence of metabolic syndrome and NAFLD. This phenomenon will contribute to an increasingly large cohort of patients that will develop NASH-related cirrhosis, decompensated liver disease and HCC. The emergence of this cohort is on the horizon and will introduce a significant disease burden in the field of liver transplantation. However, there are significant ethnic disparities in the prevalence and association of obesity with development of NASH. Furthermore, it is not clear if the risk factors associated with development of NASH and progression to cirrhosis and HCC vary by ethnicity. Our current focus on Asian populations clearly indicate that despite having lower average BMI, Asians as a group still maintain significant risks of metabolic syndrome and NAFLD, resulting primarily from the disparately higher central adiposity and visceral fat distribution seen in this cohort. This may further contribute to relatively increased risk of NASH development. More studies are needed to identify factors that influence the ethnicity-dependent rate of hepatic histological damage and the risk of HCC in NASH patients.

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P- Reviewers: Ahmed M, Chuang WL, Czaja MJ, Laguna JC, Peltec A, Zelber-Sagi S **S- Editor**: Ma YJ
L- Editor: Roemmele A **E- Editor**: Wang CH

World Journal of Hepatology

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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4254/wjh.v6.i5.274

World J Hepatol 2014 May 27; 6(5): 274-283
ISSN 1948-5182 (online)

REVIEW

Gender and racial differences in nonalcoholic fatty liver disease

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Received November 15, 2013 Revised: December 14, 2013
Accepted: April 9, 2014
Published online: May 27, 2014

Abstract

Due to the worldwide epidemic of obesity, nonalcoholic fatty liver disease (NAFLD) has become the most common cause of elevated liver enzymes. NAFLD represents a spectrum of liver injury ranging from simple steatosis to nonalcoholic steatohepatitis (NASH) which may progress to advanced fibrosis and cirrhosis. Individuals with NAFLD, especially those with metabolic syndrome, have higher overall mortality, cardiovascular mortality, and liver-related mortality compared with the general population. According to the population-based studies, NAFLD and NASH are more prevalent in males and in Hispanics. Both the gender and racial ethnic differences in NAFLD and NASH are likely attributed to interaction between environmental, behavioral, and genetic factors. Using genome-wide association studies, several genetic variants have been identified to be associated with NAFLD/NASH. However, these variants account for only a small amount of variation in hepatic steatosis among ethnic groups and may serve as modifiers of the natural history of NAFLD. Alternatively, these variants may not be the causative variants but simply markers representing a larger body of genetic variations. In this article, we provide a concise review of the gender and racial differences in the prevalence of NAFLD and NASH in adults. We also discuss the possible mechanisms for these disparities.

Key words: Nonalcoholic fatty liver disease; Nonalcoholic steatohepatitis; Race; Gender; Prevalence; Genetic polymorphism

Core tip: According to the population-based studies, nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) are more prevalent in males and in Hispanics. Both the gender and racial ethnic differences in NAFLD and NASH are likely attributed to interaction between environmental, behavioral, and genetic factors. In this article, we provide a concise review of the gender and racial differences in the prevalence of NAFLD and NASH in adults. We also discuss the possible mechanisms for these disparities.

Pan JJ, Fallon MB. Gender and racial differences in nonalcoholic fatty liver disease. *World J Hepatol* 2014; 6(5): 274-283 Available from: URL: http://www.wjgnet.com/1948-5182/full/v6/i5/274.htm DOI: http://dx.doi.org/10.4254/wjh.v6.i5.274

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is highly associated with obesity and insulin resistance (IR) and represents a spectrum of liver injury ranging from simple steatosis with a more benign course to nonalcoholic steatohepatitis (NASH) which may progress to advanced fibrosis and cirrhosis[1,2]. According to the National Health and Nutrition Examination Survey (NHANES), 33.8% and 23.7% of the United States (US) adults are obese and have metabolic syndrome, respectively[3,4]. Due to the worldwide epidemic of obesity, NAFLD has become the most common cause of elevated liver enzymes with

Table 1 Prevalence rates of nonalcoholic fatty liver disease from population-based studies

Ref.	Study population	*n*	Definition of NAFLD	Prevalence of NAFLD				
				Overall	NHW	Hispanic	NHB	Others
Ruhl *et al*[11]	NHANES Ⅲ (1988-1994)	5724	ALT[1]	2.8%	2.6%	8.4%	1.9%	3.1%
Clark *et al*[12]	NHANES Ⅲ (1988-1994)	15676	ALT or AST[2]	5.4%	4.8%	9.9%	4.2%	
Browning *et al*[13]	Dallas Heart Study	2287	MRS[3]	31%	33%	45%	24%	
Ioannou *et al*[15]	NHANES (1999-2002)	6823	ALT or AST[4]	8.1%				
Younossi *et al*[17]	NHANES Ⅲ (1988-1994)	11613	Ultrasound	18.8%				
Lazo *et al*[18]	NHANES Ⅲ (1988-1994)	12454	Ultrasound	19%	17.8%	24.1%	13.5%	
Schneider *et al*[19]	NHANES Ⅲ (1988-1994)	9675	Ultrasound		12.5%	21.2%	11.6%	
Smits *et al*[20]	NHANES Ⅲ (1988-1994)	3846	Ultrasound	30.2%	29.8%	39.4%	23.1%	
Liangpunsakul *et al*[22]	NHANES Ⅲ (1988-1994)	4376	ALT[2]	4.5%				

[1]ALT > 43 U/L; [2]ALT > 40 U/L and AST > 37 U/L for men; ALT and AST > 31 U/L for women; [3]Hepatic triglyceride content > 5.5%; [4]ALT > 43 U/L or AST >40 U/L. NHANES: National Health and Nutrition Examination Survey; NAFLD: Nonalcoholic fatty liver disease; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; MRS: Magnetic resonance spectroscopy; NHW: Non-Hispanic whites; NHB: Non-Hispanic blacks.

prevalence rates ranging from 2.8% to 46%[5,6]. Individuals with NAFLD and NASH, especially those with metabolic syndrome, have higher overall mortality, cardiovascular mortality, and liver-related mortality compared with the general population[7-9]. Liver cirrhosis secondary to NAFLD is now the second most common indication for liver transplantation in obese patients[10].

Among different racial and ethnic populations in the US, Hispanics (predominantly of Mexican origin) are at particular risk for NAFLD and tend to have a more aggressive disease course[11-20]. Hispanics accounted for nearly 50% of the US population growth from 2000 to 2010 and are projected to reach 30% of the US population within the next three decades[21]. Given the increasing prevalence and the expected growth in the Hispanic population, NAFLD poses a huge threat to the US health care system.

In this article, we provide a concise review of the gender and racial differences in the prevalence of NAFLD and NASH in adults. We also discuss the possible mechanisms for the racial/ethnic disparities, with a special focus on the Hispanics.

PREVALENCE OF NAFLD IN GENERAL POPULATIONS

The prevalence of NAFLD varies depending on the study population and the diagnostic tool used to determine the condition. The prevalence rates of NAFLD in the US based on population-based studies are summarized in Table 1. Most of these studies were based on the third NHANES (1988-1994) data. Defined as elevated alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), NAFLD was prevalent in 2.8%-5.4% of the US population[11,12,22]. From 1999 to 2002, the prevalence of NAFLD in the US further increased to 8.1%[15]. The differences of the prevalence between the two periods could be due to differences in assay methodology. Serum specimens were initially frozen after collection and then thawed prior to assay during the earlier period (1988-1994) whereas sera were only refrigerated before testing during the later time (1999-2002). Freezing serum specimens to -20 ℃ has been shown to lead to a 46% loss of ALT activity, whereas refrigerating serum specimens to 4 ℃ only led to a 6% loss[23]. Therefore, more individuals could have been falsely stratified as having normal liver enzymes and hence lower prevalence of NAFLD in the earlier period. On the other hand, true differences may exist as there was an increase in the prevalence of predictors for elevated ALT such as higher body mass index (BMI) and waist circumference between the periods 1988-1994 and 1999-2002[15]. Nevertheless, studies relying on elevated liver enzymes probably underestimate the true prevalence of NAFLD as normal ALT level provides little diagnostic or prognostic value when assessing persons for NAFLD. In the Dallas Heart Study, 79% of the subjects with hepatic steatosis had normal ALT levels (defined as ALT $\leqslant$ 40 U/L for men and $\leqslant$ 31 U/L for women)[13].

Using ultrasonography as the diagnostic tool for NAFLD, recent studies reported prevalence rates of 18.8%-30.2% in the US (Table 1)[17-20]. Ultrasonography has been used in two studies to assess the prevalence of hepatic steatosis in non-US populations. The first study performed 25 years ago reported that fatty liver was found in 14% of the population in Okinawa, Japan[24]. The second study reported that NAFLD was present in 20% of the residents who live in Northern Italy (the Dionysos study)[25]. The lower prevalence of hepatic steatosis found in the Japanese study likely reflects the low frequency or absence of obese or diabetic subjects in the study cohort[13]. Despite being more sensitive than liver enzymes for the detection of NAFLD, ultrasonography has its own limitation due to a low sensitivity for detection of mild hepatic steatosis (less than 30%)[26]. Therefore, ultrasonography also likely underestimates the true prevalence of NAFLD in general populations. Using a more sensitive magnetic resonance spectroscopy technique for measuring fat content, 31% of the participants in the Dallas Heart Study had hepatic steatosis, defined as hepatic triglyceride content greater than 5.5%[13].

NAFLD occurs in non-obese and non-overweight (defined as BMI < 25 kg/m^2) persons as well. Based on the third NHANES data, 7% of the lean individuals have

Table 2 Gender difference in the prevalence of nonalcoholic fatty liver disease from population-based studies

Ref.	Study population	*n*	Definition of NAFLD	Prevalence of NAFLD	
				Men	Women
Ruhl *et al*[11]	NHANES Ⅲ (1988-1994)	5724	ALT[1]	4.3%	1.6%
Clark *et al*[12]	NHANES Ⅲ (1988-1994)	15676	ALT or AST[2]	5.7%	4.6%
Browning *et al*[13]	Dallas Heart Study	734[5]	MRS[3]	42%	24%
Ioannou *et al*[15]	NHANES (1999-2002)	6823	ALT or AST[4]	13.4%[6]	4.5%[6]
Lazo *et al*[18]	NHANES Ⅲ (1988-1994)	12454	Ultrasound	20.2%	15.8%
Schneider *et al*[19]	NHANES Ⅲ (1988-1994)	4037[5]	Ultrasound	15%	10.1%

[1]ALT > 43 U/L; [2]ALT > 40 U/L and AST > 37 U/L for men; ALT and AST > 31 U/L for women; [3]Hepatic triglyceride content > 5.5%; [4]ALT > 43 U/L or AST >40 U/L; [5]Non-Hispanic white only; [6]Not adjusted for alcohol consumption or hepatitis C antibody status. NHANES: National Health and Nutrition Examination Survey; NAFLD: Nonalcoholic fatty liver disease; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; MRS: Magnetic resonance spectroscopy.

NAFLD compared to 28% of the overweight-obese population[17]. In the Dionysos study, hepatic steatosis on ultrasound was present in 16% of the non-obese participants[27]. In a Japanese study, ultrasonographic fatty liver was found in 11.2% of non-obese persons during voluntary health check-up[28].

PREVALENCE OF NASH IN GENERAL POPULATIONS

Liver biopsy is the current suboptimal standard for the diagnosis and staging of NASH, but invasiveness and cost preclude its use as a screening tool in general populations[29]. The population prevalence of NASH has therefore been difficult to establish since it is unethical to biopsy asymptomatic persons in the community. Among 351 apparently nonalcoholic patients, a Canadian autopsy study from the late 1980s found that NASH was present in 2.7% of lean patients and in 18.5% of markedly obese patients[30]. More recently, two Asian studies reported similar prevalence of NASH in 1.1%-2.2% of living donors before liver transplantation[31,32]. Based on the third NHANES data, 2.6% of the US population have NASH defined as the presence of moderate-severe hepatic steatosis by ultrasound and elevated aminotransferases in the presence of type 2 diabetes or IR[17].

GENDER DIFFERENCE IN THE PREVALENCE OF NAFLD

Some old studies reported that women were at higher risk for NAFLD, but these studies were not population based and were subject to potential ascertainment bias[11]. Based on the third NHANES data, most of the studies reported that NAFLD is significantly more prevalent in men than in women (Table 2). However after dichotomizing individuals into lean and overweight-obese groups, Younossi *et al*[17] reported that the lean NAFLD cohort was more commonly female. Using data from 698 patients from the well characterized NASH Clinical Research Network (CRN), patients with biopsy proven NASH were more likely to be female than male in a roughly 2:1 ratio; possibly reflecting a higher disease burden in women or, alternatively, sex differences among those pursuing and receiving healthcare[33]. Together, these findings highlight uncertainties regarding the influence of gender on NAFLD.

A number of mechanisms may contribute to gender differences in the prevalence of NAFLD.

The role of IR, which is closely associated with NAFLD[1,2], remains controversial. Ruhl *et al*[11] reported that NAFLD was more prevalent in men than in women (4.3% *vs* 1.6%, respectively), a finding essentially explained by the higher waist-to-hip circumference (WHR) ratio in men. WHR is correlated with visceral adipose tissue (VAT) and visceral adiposity is associated with both peripheral and hepatic IR[34,35]. In another study using the same database but different cohort size, Clark *et al*[12] also reported that men have higher prevalence of NAFLD than women (5.7% *vs* 4.6%, respectively), although there was no significant difference in either gender in IR as calculated by homeostasis model assessment (HOMA) or exercise level. Moreover, in the Dallas Heart Study, non-Hispanic white men had an approximately 2-fold higher prevalence of hepatic steatosis than white women. Differences in body weight or insulin sensitivity measured by HOMA did not explain these sex differences.

Alcohol use is another possible explanation for gender differences in NAFLD. In the Dallas Heart Study, white men who reported moderate ethanol intake had a significantly higher prevalence of hepatic steatosis than female counterparts (42% *vs* 20%, $P = 0.03$). In fact, moderate alcohol intake was associated with an decrease in the prevalence of hepatic steatosis in women[13]. Similarly, Schneider *et al*[19] reported that non-Hispanic white men, who were more likely to be self-defined as "low current drinkers" (men ⩽ 2 drinks/d; women ⩽ 1 drink/d), had a significantly higher prevalence of NAFLD than non-Hispanic white women (15% *vs* 10.1%, respectively), even after adjusting for BMI and waist circumference. Finally, in adult members of the Kaiser Permanente Medical Care Program in California, NAFLD was 3.5 times more common in Asian men than in Asian women ($P = 0.016$). There was no significant difference in BMI (> 28 kg/m^2), diabetes mellitus, dyslipidemia, or current alcohol use between Asian men and women, but 68% of Asian men were previous drinkers, compared with 17% of Asian

women ($P < 0.02$)[14]. Together, these studies suggest an effect of alcohol consumption on gender differences in the prevalence of NAFLD. Whether differences in hepatic metabolism of alcohol between men and women also contribute to the gender difference in not fully defined[19].

Other factors, including lifestyle and sex hormone may also influence the gender difference in the prevalence of NAFLD. In one study, individuals with NAFLD had similar degrees of IR and obesity to those without, but males with NAFLD consumed more non-diet soda on a weekly basis (54.4% *vs* 34%, $P = 0.037$)[16]. Another recent study showed that prevalence of NAFLD was similar in pre- and intrapubertal boys and higher in the postpubertal groups (51.2%), whereas in girls NAFLD was most common in the intrapubertal group (25.2%) and lower in the postpubertal group (12.2%)[36].

RACIAL/ETHNIC DIFFERENCES IN NAFLD AND NASH

Despite using different diagnostic tools, US population-based studies all found that Hispanics have the highest and non-Hispanic blacks have the lowest prevalence of NAFLD (Table 1). Echoing the racial/ethnic differences in the NAFLD prevalence, Younossi *et al*[17] recently reported that NASH was independently associated with being Hispanic [odds ratio (OR), 1.72; 95%CI: 1.28-2.33] and inversely associated with being African-American (OR, 0.52; 95%CI: 0.34-0.78). Each of these studies is limited by the fact that NASH was diagnosed by imaging and/or biochemical criteria rather than by histology.

Single center studies show that ethnicity may also influence NAFLD histology. For instance, African Americans were found to have less steatosis than whites. Asians and Hispanics showed higher grades of ballooning and Mallory bodies, respectively, than whites and other ethnicities combined[37]. Williams *et al*[16] also reported a significantly higher prevalence of NASH in Hispanics than Caucasians (19.4% *vs* 9.7%, $P = 0.03$) although comparison of demographics such as BMI between different ethnic groups were not available in this study. However, Kallwitz *et al*[38] found no significant differences in hepatic steatosis, NASH, or liver fibrosis (≥ F2) between morbidly obese Hispanic and non-Hispanic white patients receiving bariatric surgery. Similar to the other reports, morbidly obese African American patients had a lower rate of NAFLD, NASH and less fibrosis than non-Hispanic whites and Hispanics. Moreover, in a NASH CRN study consisting mainly of Caucasian subjects (82%), subjects of Hispanic ethnicity overall had lower fibrosis scores and less advanced fibrosis[33]. Finally, in an analysis restricted to 3082 individuals with normal weight (BMI 18.5-24.9 kg/m^2), Schneider *et al*[19] found no significant racial differences in the fully adjusted logistic regression model for NAFLD; however, Mexican Americans remained significantly more likely to have NAFLD with elevated aminotransferases (OR, 3.4; 95%CI: 1.29-7.18). This finding was confirmed in a prospective study where overweight or obese Hispanics and Caucasians had similar hepatic or adipose tissue IR and severity of NASH by histology when matched for major clinical variables, in particular for total body fat[39]. These findings suggest that a component of the higher prevalence of NAFLD and NASH observed in Hispanics may be attributed to differences in the frequency of major clinical variables such as components of metabolic syndrome or diabetes that influence the development of NAFLD.

MECHANISMS FOR THE RACIAL/ETHNIC DIFFERENCES IN NAFLD AND NASH

A number of potential factors have been implicated in racial and ethnic differences in NAFLD. These include differences in lifestyle, IR, distribution of adiposity and genetics. These factors are not mutually exclusive and may occur and act in concert.

Lifestyle

According to the "two hit" theory, steatohepatitis development requires a double hit, the first producing steatosis, and the second a source of oxidative stress capable of initiating significant lipid peroxidation[40]. Dietary habits may promote steatohepatitis directly by modulating hepatic triglyceride accumulation and antioxidant metabolism as well as indirectly by affecting insulin sensitivity and postprandial triglyceride metabolism[41]. Several studies have reported that different racial and ethnic groups have substantial differences in their diet. In an early US population-based study (1987 National Health Interview Survey), Hispanics reported higher energy and carbohydrate intakes and a lower percentage of energy from fat than blacks or whites (35.6%, 38.4%, and 38.7% of energy from fat for Hispanics, blacks, and whites, respectively). Whites had lower cholesterol intake than the other two groups, and blacks had a higher intake of sweets[42]. According to the San Antonio heart study published almost 20 years ago, when data were pooled across socioeconomic groups, Mexican Americans consumed more carbohydrate, saturated fat, and cholesterol, and less linoleic acid than Anglo Americans. However, there were no ethnic differences in total fat, saturated fat, or carbohydrate consumption when compared within a given socioeconomic status[43]. Data from the Stanford Five-City Project showed that low educated white adults consumed significantly more fat as measured by percentage of calories from total fat (37.7% *vs* 33.3%) and saturated fat (13.7% *vs* 11.8%), and consumed significantly less dietary carbohydrate (45.5% *vs* 49.7%) and fiber (17.1 g *vs* 26 g) than Hispanic adults. Interestingly, a graded relationship was found between acculturation and dietary measures, where more acculturated Hispanics (English-speaking) were intermediate between less acculturated Hispanics (Spanish-speaking) and whites in their dietary intake[44].

Common theme in these studies is that Hispanics consume more carbohydrates than other ethnic groups.

The role of excess carbohydrate intake in NASH has been shown in at least two other studies[45,46]. In the first study of a small series of Japanese adults, individuals with histology proven NASH had a higher intake of simple carbohydrates than those with simple steatosis[44]. In the second study from the NASH CRN, Hispanics with NASH had higher carbohydrate intake compared to non-Hispanic whites with NASH[45]. In addition to high carbohydrate diet, NASH is also associated with a low intake of zinc and lower ratio of intake of polyunsaturated fatty acid to saturated fatty acid[44].

Analysis of the NASH CRN data further showed that patients with NAFLD ate at fast-food restaurants (≥ 1 per week) more often (70.9% *vs* 60.5%, $P = 0.049$) and exercised (≥ 30 min per week) less frequently (56.3% *vs* 68.9%, $P = 0.02$) than their non-NAFLD counterparts. However, racial differences in these two measures was not studied[16]. A recent study based on the NHANES data reported that sedentary individuals had a significantly higher prevalence of NAFLD independent of other risk factors[18]. In a small series of 37 patients, Krasnoff *et al*[47] reported that patients with NAFLD of differing histological severity have suboptimal cardiorespiratory fitness, muscle strength, body composition, and physical activity participation. These findings establish the association between physical inactivity and NAFLD and support the current recommendation of regular exercise for patients with the condition.

IR

Several US and non-US population-based studies have shown that NAFLD is highly associated with central obesity, IR, and components of metabolic syndrome (high triglyceride, low high-density-lipoprotein cholesterol, hyperglycemia, and hypertension)[11-13,15,18,22,25,48]. NAFLD has therefore been suggested to be a hepatic feature of the metabolic syndrome[49]. However, Smits *et al*[20] recently challenged this popular notion. In their study, NAFLD was strongly related to the different components of the metabolic syndrome. However, adding hepatic steatosis to a mathematical model containing the traditional components of the metabolic syndrome did not improve goodness of fit and if anything resulted in a decrease in model fit. They thus concluded that NAFLD is not an independent additional component or manifestation of the metabolic syndrome.

In addition to being a lipid storage compartment, adipose tissue is also an endocrine organ[50]. Adipose tissue IR plays key role in the development of metabolic and histological abnormalities of obese patients with NAFLD. Liver steatosis was rare in metabolically healthy obese subjects with normal adipose tissue insulin sensitivity. Compared to patients without steatosis, patients with NAFLD were insulin resistant at the level of adipose tissue, liver, and skeletal muscle. Metabolic parameters, hepatic IR, and liver fibrosis but not necroinflammation deteriorated as adipose tissue IR worsened[51]. The coincident occurrence of hepatic steatosis and IR has led to the hypothesis that excess triglyceride in liver causes IR[52]. This notion was challenged by a recent study by Lomonaco *et al*[39]. In that study, liver fat was slightly, but not significantly, higher in Hispanic than Caucasian patients. This slightly higher liver fat content was not associated with worse hepatic or adipose tissue IR[39].

As shown in Table 1, Hispanics have a higher prevalence and blacks have a lower prevalence of NAFLD than whites. According to the data from the third NHANES, both black and Mexican American women had higher cardiovascular disease risk factors such as hypertension, physical inactivity, higher BMI and diabetes than white women of comparable socioeconomic status[53]. While the higher prevalence of hepatic steatosis in Hispanics can be explained by the high prevalence of obesity and IR in this population, the lower prevalence of hepatic steatosis in blacks cannot be explained by the same reason. In the Insulin Resistance Atherosclerosis Study, African Americans were more insulin resistant than Hispanics. Hispanics however had higher prevalence of NAFLD than African Americans (24% *vs* 10%)[54]. Therefore an IR paradox may exist[55]. It has been hypothesized that differences in NAFLD and NASH by race may result from differences in the distribution of adiposity (*e.g.*, subcutaneous *vs* visceral) or differences in triglycerides because blacks have relatively less VAT and lower triglycerides than Hispanics[19,56]. In addition, African Americans may be more resistant to both the accretion of triglyceride in the abdominal visceral compartment (adipose tissue and liver) and hypertriglyceridemia associated with IR[55].

Distribution of adiposity

Several studies have reported racial differences in the distribution of adiposity, especially in women. In a small study of age- and weight-matched healthy women (8 black and 10 white), black women had 23% less VAT as measured by computed tomography (CT) than white women. In addition, black women had significantly lower plasma glucose and triglycerides and significantly higher plasma high-density-lipoprotein cholesterol[57]. Based on the Dallas Heart Study data, blacks had less intraperitoneal fat as measured by magnetic resonance imaging and more lower extremity fat than their Hispanic and Caucasian counterparts, despite controlling for age and total adiposity. In that study, the prevalence of IR was similar between blacks and Hispanics who had the highest levels of intraperitoneal fat and liver fat. Furthermore, insulin levels and HOMA values were the highest and serum triglyceride levels were lowest among blacks after controlling for intraperitoneal fat[55]. In a prospective study of healthy sedentary women, Casas *et al*[58] found that Hispanic women had greater total adiposity than white women, which was primarily the result of higher percentage fat and fat mass in the trunk. Within the trunk region, abdominal and subscapular skinfold thicknesses were 30%-40% significantly greater in the Hispanic women. Total fat-free mass was slightly but significantly lower in the Hispanic women primarily due to a smaller fat-free

mass in the trunk region. In a study involving healthy subjects, Asians despite of having lower BMI had more upper-body subcutaneous fat as measured by dual-photon absorptiometry than did whites. The magnitude of differences between the two races was greater in females than in males[59]. A later study with a smaller cohort reported that Asian American premenopausal women had higher VAT than European American women, after adjusting for age and total body fat. There was a significant age by race interaction such that race differences in VAT were more evident over the age of 30 years. No differences in VAT could be detected between Asian American and European American men, even after adjusting for potential covariates[60]. Visceral adiposity has been reported to be associated with both peripheral and hepatic IR, independent of gender, in diabetic patients[35]. Visceral fat has also been shown as an important site for interleukin-6 secretion and provides a potential mechanistic link between visceral fat and systemic inflammation in people with abdominal obesity[61]. Inflammatory activation within metabolic tissues such as white adipose tissue, liver, and skeletal muscle potentiates IR and metabolic disease[62].

Together, these results support that differences in distribution of adiposity may influence racial differences in the prevalence of NAFLD and NASH.

Genetic variations

Caldwell *et al*[63] previously proposed that obesity and IR are often "essential but not sufficient" in the development of NAFLD given the variable prevalence of steatosis in different ancestry groups. They further suggested a genetic basis for the variable presence of steatosis in the metabolic syndrome. Possible mechanisms to explain this variation include differences in hepatic fatty acid-binding protein (influencing fatty acid import to the liver), in the activity of microsomal triglyceride transfer protein (influencing *de novo* fat synthesis), or in other compensatory mechanisms that are active in insulin-resistant patients without steatosis. The findings of familial clustering of NAFLD and NASH suggest a hereditary component for the conditions. Struben *et al*[64] retrospectively examined 8 index patients who had either NASH with or without cirrhosis or cryptogenic cirrhosis and 10 of their relatives from 8 kindreds. They found that co-existence of NASH and/or cryptogenic cirrhosis in 7 of 8 kindreds studied. Willner *et al*[65] reviewed 90 patients with NASH and found that 16 (18%) of the patients came from 9 families with NASH. Two generations were involved in 6 families and siblings were involved in the other 3 families. Notably, cirrhosis was observed in 7 of these 9 families. A small case series from Japan reported 3 families each with 2 members with biopsy-proven NASH[66]. By studying overweight children with and without biopsy-proven NAFLD and their families, Schwimmer *et al*[67] reported that fatty liver was significantly more common in siblings (59% *vs* 17%) and parents (78% *vs* 37%) of children with NAFLD than those without NAFLD. In addition to genetic basis, sharing common environmental factors and/or lifestyles could be alternative explanations for the familial nature of NAFLD and NASH.

In the landmark study from the Dallas Heart Study, Romeo *et al*[68] first reported that the rs738409[G] allele in patatin-like phospholipase domain-containing 3 (*PNPLA3*) gene was strongly associated with hepatic fat content even after adjustment for BMI, diabetes status, ethanol use, as well as ancestry. The variant is a cytosine to guanine substitution that changes codon 148 from isoleucine to methionine (I148M). Hepatic fat content was more than twofold higher in the G allele homozygotes than in noncarriers. The frequencies of the G allele were concordant with the relative prevalence of NAFLD in the three ancestry groups; the highest frequency of allele was in Hispanics (0.49), with lower frequencies observed in European Americans (0.23) and African Americans (0.17). In the Dallas Heart Study, rs738409(G) was significantly associated with ALT and AST levels only in Hispanics. Interestingly, rs738409(G) was not associated with BMI or indices of insulin sensitivity such as fasting plasma glucose and insulin concentrations or HOMA. Furthermore, *PNPLA3* genotype was not associated with concentrations of triglyceride, total cholesterol, high-density-lipoprotein cholesterol or low-density-lipoprotein cholesterol. Another variant of the *PNPLA3* [rs6006460(T), encoding S453I] was found to be associated with lower hepatic fat in African Americans. Regression analysis indicated that these two sequence variations accounted for 72% of the observed ancestry-related differences in hepatic fat content in the Dallas Heart Study.

Similar to the Dallas Heart Study, Wagenknecht *et al*[69] also found a higher frequency of *PNPLA3* rs738409(G) in Hispanics in a large US minority cohort (843 Hispanic Americans and 371 African Americans) study. The G allele was two times more common in Hispanic Americans than in African Americans (40% *vs* 19%), consistent with the greater prevalence of NAFLD in Hispanic Americans (24% *vs* 9%). The G allele was also associated with elevated ALT and AST but not metabolic phenotypes in both Hispanic- and African Americans. However, unlike the Dallas Heart Study, the *PNPLA3* genotype could only explain 4.4% of variation in liver fat content in Hispanic Americans and 5.6% in African Americans. Even with adjustment for the *PNPLA3* variation, a significant ethnic disparity in liver fat content persisted. It was therefore suggested that *PNPLA3* does not explain the unusually high prevalence of NAFLD in Hispanic Americans.

The *PNPLA3* genotype is associated with hepatic fat content and aminotransferase in non-US populations as well. In a Finnish study, 291 individuals were genotyped and had liver fat measured by magnetic resonance spectroscopy. The G allele was associated with increased liver fat content and AST independently of age, sex, and BMI. *PNPLA3* expression in the liver was positively related to obesity and to liver fat content in persons who were not morbidly obese (BMI < 40 kg/m^2)[70]. In another study, 678 obese (mean BMI = 41 kg/m^2) Italians were genotyped for the *PNPLA3* variant. It was found that ALT

and AST were significantly higher in carriers of the G allele; 50% of the individuals homozygous for the G allele had elevated ALT (> 40 U/L) compared with 25% of the carriers of two C alleles, whereas 30% of the heterozygotes had elevated ALT. Glucose tolerance and insulin sensitivity were similar in all three genotypes[71]. In a Latin American study, 172 Argentinians with NAFLD defined by ultrasonographic steatosis and 94 controls were genotyped. Similar to the previous reports, rs738409[G] was significantly associated with NAFLD, independent of age, sex, BMI, and HOMA index. Patients with CC genotype had a lower histologic steatosis score (14.9% ± 3.9%) in comparison with the CG genotype (26.3% ± 3.5%) and GG genotype (33.3% ± 4%) ($P < 0.005$). Similar to the previous US minority cohort study[69], the *PNPLA3* genotype could only account for a small amount (5.3%) of the total variation in hepatic steatosis[72].

The *PNPLA3* genotype exerts a strong influence not only on liver fat accumulation but also on the susceptibility of a more aggressive disease course. A recent meta-analysis of 16 studies concluded that the GG homozygotes had 3.24-fold greater risk of higher necroinflammatory scores and 3.2-fold greater risk of developing fibrosis when compared with the CC homozygotes (data from 1739 and 2251 individuals, respectively). NASH was more frequently observed in the GG than the CC homozygotes (OR, 3.488; 95%CI: 1.859-6.454; data from 2124 patients). In the meta-analysis, a negative correlation between the male proportion in the studied population and the effect of rs738409 on liver fat content was observed, suggesting that a sexual dimorphism might be involved in the effect of the single nucleotide polymorphism (SNP) on NAFLD development. The rs738409 GG genotype versus CC genotype was associated with a 28% increase in ALT levels. The *PNPLA3* rs738409 was therefore proposed as a strong modifier of the natural history of NAFLD[73].

In addition to *PNPLA3*, the Genetics in Obesity-related Liver Disease (GOLD) Consortium studied 7176 individuals of European ancestry and identified genetic variants in or near three novel loci [neurocan gene *NCAN* (rs2228603), glucokinase regulatory protein gene *GCKR* (rs780094), and lysophospholipase-like 1 gene *LYPLAL1* (s12137855)] that were associated with both increasing CT hepatic steatosis and histologic NAFLD. The genetic variant in or near glycogen binding subunit of protein phosphatase 1 gene *PPP1R3B* (rs4240624) was associated with CT steatosis but not histologic NAFLD. Variants at these 5 loci exhibited distinct patterns of association with serum lipids, as well as glycemic and anthropometric traits. Specifically variants in or near *NCAN*, *GCKR*, and *PPP1R3B* associated with altered serum lipid levels, whereas those in or near *LYPLAL1* and *PNPLA3* did not. Variants near *GCKR* and *PPP1R3B* also affected glycemic traits. These findings suggest development of hepatic steatosis, NASH/fibrosis, or abnormalities in metabolic traits are probably influenced by different metabolic pathways and may provide new insights that into how obesity can lead to metabolic complications in some but not all individuals[74]. The observed genetic variants in European ancestry individuals were recently characterized in a multi-cohort study of African- ($n = 3124$) and Hispanic Americans ($n = 849$)[75]. In that study, variants in or near *PNPLA3*, *NCAN*, *GCKR*, *PPP1R3B* in African Americans and *PNPLA3* and *PPP1R3B* in Hispanic Americans were significantly associated with CT hepatic steatosis. *LYPLAL1* was not significantly associated with hepatic steatosis in either African- or Hispanic Americans despite comparable allele frequencies. The association of *NCAN* with hepatic steatosis was in an opposite direction in Hispanic Americans, suggesting it would have a small protective effect in this population. The allele frequency and effect size of each variant varied across ancestries. For example, the effect size of *PNPLA3* rs738409 was similar across the ancestries and the frequency of the G allele was higher in Hispanics. The effect size of *PPP1R3B* rs4240624 was twice in European ancestry individuals than other ancestries, whereas its frequency was roughly the same across the three ethnic groups. *GCKR* rs780094 had the same effect across ancestries but its frequency in African Americans was half of that in European ancestry individuals and Hispanic Americans, which were about equal[75].

Finally, in a recent multi-ethnic ($n = 4804$) study from the third NHANES, Hernaez *et al*[76] attempted to replicate the findings of the GOLD Consortium. Similar to the previous report by Palmer *et al*[75], the G allele of *PNPLA3* rs738409 was more prevalent in Mexican Americans than non-Hispanic whites and blacks. However, the T allele of *GCKR* rs780094 and the A allele of *PPP1R3B* rs4240624 were more common in non-Hispanic whites than the other two ethnic groups. In contrast to the GOLD Consortium, several discrepancies were noted. First of all, the *PNPLA3* variant was associated with hepatic steatosis diagnosed by ultrasonography only among Mexican Americans. Secondly, *NCAN* and *PPP1R3B* regions were associated with hepatic steatosis only in non-Hispanic whites. Thirdly, neither *LYPLAL1* nor *GCKR* were associated with hepatic steatosis in the third NHANES population. Fourthly, *PNPLA3* and *GCKR* were the only variants associated with elevated ALT (> 30 U/L in men and > 19 U/L in women) and the association in non-Hispanic whites only[76]. In an editorial comment, Browning called for the following considerations when interpreting the data of Hernaez *et al*[76]. The true prevalence of fatty liver in the study population might be higher than reported and/or that some individuals might have been mistakenly classified as having NAFLD since ultrasound is not as sensitive or specific for hepatic steatosis as other imaging modalities. In addition, the study appears to be underpowered to examine associations across ethnic/racial groups, especially for SNPs with a low allelic frequency. If underpowered, the analysis would be prone to false-negative results[77].

Variants in other genes such as cytochrome P450 2E1[78] and apolipoprotein C3[79] have been reported to be

implicated in NAFLD. To provide a detailed review of other genetic variants in NAFLD is beyond the scope of this review.

CONCLUSION

According to the population-based studies, NAFLD and NASH are more prevalent in males and in Hispanics. The gender differences in NAFLD and NASH can be probably explained by gender disparities in body fat distribution, lifestyle, and sex hormone metabolism. The racial/ethnic differences in NAFLD and NASH are likely attributed to interaction between environmental, behavioral, and genetic factors. Despite having similar or worse insulin sensitivity, non-Hispanic blacks are less likely to have NAFLD/NASH than non-Hispanic whites and Hispanics. Racial differences in body fat distribution and lipid metabolism may explain the IR paradox. By using genome-wide association study, several SNPs have been identified to be associated with NAFLD/NASH. These genetic variants however only account for a small amount of variation in hepatic steatosis among ethnic groups and may serve as modifiers of the natural history of NAFLD. As suggested by Browning[77], these trait-associated SNPs may not be the causative genetic variants but simply tags representing a larger body of SNPs. Further study is required to define how these variants alter normal physiology and/or identify the functional genetic variant in the haplotype block represented by the SNP[77].

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P- Reviewers: Claria J, Gara N, Nagarajan P, Rostami-Nejad M
S- Editor: Gou SX **L- Editor**: A **E- Editor**: Wang CH

World Journal of Hepatology

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DOI: 10.4254/wjh.v6.i5.284

World J Hepatol 2014 May 27; 6(5): 284-292
ISSN 1948-5182 (online)

REVIEW

Chronic hepatitis B: Advances in treatment

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Received: November 12, 2013 Revised: January 7, 2014
Accepted: March 13, 2014
Published online: May 27, 2014

Abstract

Treatment of chronic hepatitis B (CHB) has markedly improved in the last 15 years due to the availability of direct antivirals which greatly increase therapeutic options. Currently, there are two classes of agents licensed for CHB treatment: standard or pegylated interferon alpha (IFN or Peg-IFN) and five nucleoside/nucleotide analogues (NAs). Long-term treatment with NAs is the treatment option most often used in the majority of CHB patients. Entecavir and tenofovir, the most potent NAs with high barrier to resistance, are recommended as first-line monotherapy by all major treatment guidelines and can lead to long-lasting virological suppression, resulting in histological improvement or reversal of advanced fibrosis and reduction in disease progression and liver-related complications. In this review, we focus on current treatment strategies of chronic hepatitis B and discuss the most recent efficacy and safety data from clinical trials and real life clinical practice. Recent findings of response-guided approaches are also discussed.

Key words: Chronic hepatitis; Antiviral therapy; Peg-interferon; Nucleos(t)ide analogues; Antiviral resistance

Core tip: Patients with chronic hepatitis B are a heterogeneous population and require different management strategies. In clinical practice, several baseline factors, related to the patient, drug, stage of liver disease, comorbidities, lifestyle factors, coinfections and profile of hepatitis B virus infection, should be taken into consideration in order to individually optimize therapy. Surface antigen of the hepatitis B virus quantification is a potential new biomarker for treatment individualization and response-guided therapy. In the last two decades, the availability of potent oral antivirals changed the natural history of chronic hepatitis B; however, the risk of hepatocellular carcinoma (HCC) has not been abolished and thus regular HCC surveillance in high risk patients is required.

Santantonio TA, Fasano M. Chronic hepatitis B: advances in treatment. *World J Hepatol* 2014; 6(5): 284-292 Available from: URL: http://www.wjgnet.com/1948-5182/full/v6/i5/284.htm DOI: http://dx.doi.org/10.4254/wjh.v6.i5.284

INTRODUCTION

Chronic infection with hepatitis B virus (HBV) is a major health problem worldwide, affecting approximately 350 million people, and is the leading cause of chronic liver disease, cirrhosis and hepatocellular carcinoma (HCC), accounting for over 1 million deaths annually[1].

The goal of chronic hepatitis B (CHB) treatment is to prevent or reduce the development of cirrhosis, end-stage liver disease, HCC and, ultimately, liver-related death. Several studies have shown that the risk of disease progression is reduced by means of sustained suppression of viral replication[2-4]. Furthermore, maintaining viral suppression increases the rate of hepatitis B surface antigen (HBsAg) clearance, which is the ideal end-point of antiviral treatment as it is associated with a definite remission of chronic hepatitis B activity and an improved long-term outcome. However, even if HBsAg loss occurs, HBV cannot be completely eradicated by treatment due to the persistence of the so-called covalently closed

Table 1 European Association for the Study of the Liver guidelines compared to other international guidelines

Criteria	EASL 2012[6]	AASLD 2009[7]	APASL 2012[8]
HBV DNA treatment threshold			
HBeAg(+) (IU/mL)	2000	20000	20000
HBeAg(-) (IU/mL)	2000	2000-20000	2000
ALT treatment threshold	> ULN	> 2 × ULN	> 2 × ULN
Liver biopsy	Moderate to severe necroinflammation or fibrosis	Not applicable (consider in certain groups)	

ULN: Upper limits of normal; HBeAg: Hepatitis B e antigen; ALT: Alanine aminotransferase; AASLD: American Association for the Study of Liver Diseases; APASL: Asia Pacific Association for the Study of the Liver; EASL: European Association for the Study of the Liver; HBV: Hepatitis B virus.

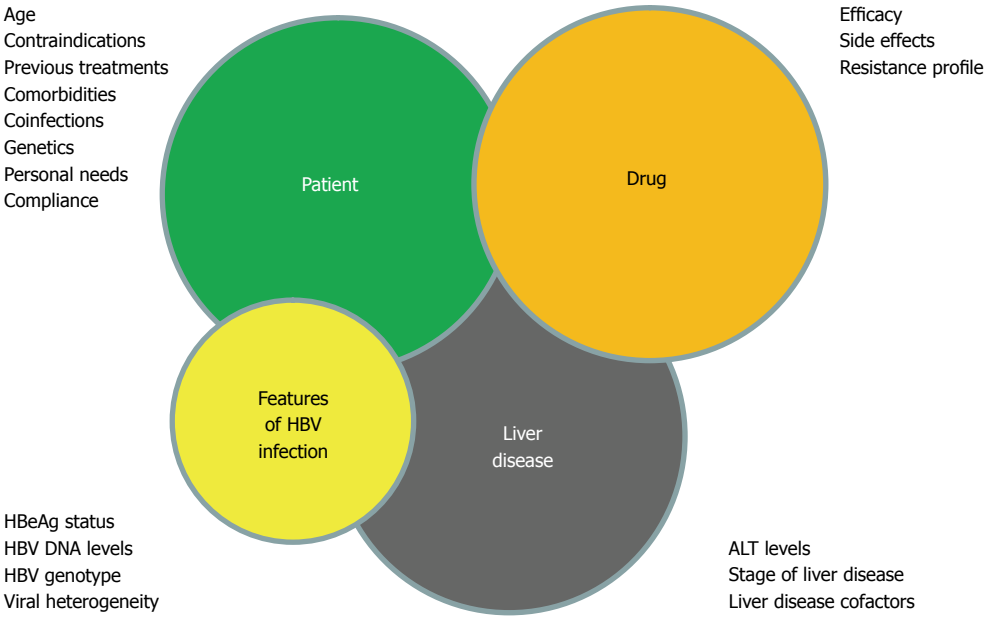

Figure 1 Management of chronic hepatitis B patient: decision making process. ALT: Alanine aminotransferase; HBeAg: Hepatitis B e antigen; ALT: Alanine aminotransferase; HBV: Hepatitis B virus.

circular DNA (cccDNA), the template for viral RNA transcription, in the nucleus of infected hepatocytes[5].

Since the introduction of interferon alpha as an initial antiviral therapy at the end of the 1980s, the treatment of CHB has markedly improved in the last 15 years due to the availability of nucleos(t)ide analogues (NAs), direct antiviral agents which have greatly increased therapeutic options and permitted the achievement of virological response in almost all patients.

In this review, we focus on current treatment strategies of chronic hepatitis B and discuss the most recent long-term NA efficacy and safety data from clinical trials and real life clinical practice.

ANTIVIRAL TREATMENT

Treatment indications

The complex interplay between viral replication and host immune response determines the natural course of chronic HBV infection which can generally be divided into four phases: immune tolerance, immune clearance, low/non replicative and reactivation phases. Liver disease is associated with immunoclearance and reactivation phases; therefore, immunotolerant and inactive carriers do not require treatment, while antiviral therapy should be reserved for HBsAg carriers with active viral replication and biochemical or histological evidence of liver damage. The criteria for identification of candidates for antiviral therapy, according to current guidelines[6-8] are shown in Table 1.

In clinical practice, however, the decision-making process is more complex as it involves several factors related to the patient (age, sex, genetics), the drug (efficacy, side effects, resistance barrier), the liver disease (fibrosis, type and extent of inflammation), the liver disease cofactors (alcohol use, diabetes, insulin-resistance, obesity), the coinfections (HDV, HCV, HIV) and the profile of HBV infection (HBeAg-status, HBV DNA levels, genotype, viral heterogeneity) (Figure 1).

The assessment of hepatic fibrosis with liver biopsy or non-invasive methods is recommended since it can assist the decision to start antiviral therapy. Treatment is mandatory for patients with severe fibrosis or cirrhosis (F3-F4) and patients with compensated or decompensated cirrhosis and detectable HBV DNA should be considered for treatment, independent of ALT levels.

Table 2 Main advantages and disadvantages of pegylated interferon alpha and nucleos(t)ides analogues in chronic hepatitis B[6]

	Peg-IFN	Nucleos(t)ides analogues
Advantages	Finite duration (usually 48 wk)	Potent antiviral effect
	Higher rates of anti-HBe and anti-HBs seroconversion with 12 mo of therapy	Excellent tolerance, good safety
	Absence of resistance	Oral administration (once daily)
		No contraindication for treatment
Disadvantages	Moderate antiviral effect	Unknown (perhaps indefinite) duration of treatment
	Inferior tolerability	Rare HBsAg loss
	Risk of adverse events	Risk of viral resistance
	Subcutaneous injections	Unknown long-term safety
	Contraindications in specific patient subgroups	

Peg-IFN: Pegylated interferon; HBsAg: Hepatitis B surface antigen.

Therapy is indicated for patients with moderate fibrosis (F2), while in those with mild or no fibrosis (F0-F1), the indication for treatment should be assessed individually, taking into account patient age, comorbidities, presence of liver disease cofactors, HDV/HCV/HIV coinfections, family history of HCC or cirrhosis, and extrahepatic manifestations.

Anti-HBV drugs

At present, there are two classes of agents licensed for the treatment of CHB: standard or pegylated interferon alpha (IFN or Peg-IFN) and five nucleoside/nucleotide analogues.

Standard IFN has been largely replaced by Peg-IFN due to the more convenient administration schedule (once weekly versus a thrice weekly subcutaneous injection), the longer half-life without wide fluctuations in serum concentrations, and a more effective viral suppression. There are two pegylated-IFN formulations: Peg-IFN alpha-2a and Peg-IFN alpha-2b which have demonstrated a similar efficacy in clinical trials, but only the former is globally licensed for treatment of CHB, while Peg-IFN alpha-2b has been approved in only a few countries. Peg-IFN is a cytokine with a dual antiviral and immunomodulatory activity and therefore has the potential for an immune-mediated control of HBV infection, thus providing the opportunity to obtain a sustained virological response after treatment discontinuation, and the possibility of inducing HBsAg loss in patients who achieve and maintain undetectable HBV DNA. IFN-based treatment, however, is often complicated by the occurrence of side effects, such as influenza-like symptoms, fatigue, neutropenia, thrombocytopenia and depression, which sometimes require dose modification and cause premature cessation of treatment[9]. Moreover, Peg-IFN is contraindicated in patients with decompensated HBV-related cirrhosis or autoimmune disease, in patients with uncontrolled severe depression or psychosis, in patients receiving immunosuppressive therapy or chemotherapy, and in female patients during pregnancy[6].

NAs are oral direct antiviral agents which specifically inhibit the viral polymerase/reverse transcriptase, an enzyme with a crucial role in the HBV life cycle. As a result, NAs block the production of new virions and progressively reduce serum HBV DNA to undetectable levels, but they have little or no effect on the cccDNA present in the nucleus of the infected hepatocytes. The persistence of the intrahepatic cccDNA determines the reactivation of HBV replication after interrupting NA treatment, thereby justifying the need for a long-term (potentially life-long) therapy for a sustained viral replication control. After lamivudine (LAM), the first nucleoside analogue approved for the treatment of CHB, another two nucleosides, telbivudine (LdT) and entecavir (ETV), and two nucleotide analogues, adefovir (ADV) and tenofovir (TDF), have gradually become available in recent years. NAs are characterized by a different antiviral potency and drug-resistance pattern, while entecavir and tenofovir are the two most potent analogues with a high barrier to resistance development.

The main advantages and disadvantages of Peg-IFN and NAs for treatment of CHB are shown in Table 2.

Treatment strategies

There are two different therapeutic strategies for both HBeAg-positive and HBeAg-negative CHB patients: short-term or "curative" treatment and long-term or "suppressive" treatment. The first strategy aims to obtain a sustained suppression of viral replication off-treatment by inducing the immune-controlled status of HBV infection which corresponds to the profile of the inactive carrier, that is, normal ALT levels coupled with HBV DNA < 2000 IU/mL and anti-HBe positivity. This strategy is IFN-based (Peg-IFN administered for 48 wk); a finite treatment with NAs is possible only in HBeAg-positive patients. The second strategy aims to obtain a rapid and long-term maintained viral suppression (HBV DNA < 10-15 UI/mL). This strategy is exclusively based on NAs.

First-line monotherapy

Peg-IFN, entecavir or tenofovir are recommended as first-line monotherapy by all major guidelines in patients with CHB or compensated cirrhosis[6-8]. The most favorable candidates for Peg-IFN are those with low HBV DNA levels, high ALT and HBV, genotype A or B rather than C or D, and those without advanced liver disease.

Entecavir or tenofovir are the only therapeutic op-

tions in patients with decompensated liver disease, in those undergoing immunosuppressive treatment or with contraindications, and those unwilling to receive Peg-IFN. As Peg-IFN can achieve a sustained off-therapy response in only a minority of cases and a proportion of patients cannot tolerate or have IFN contraindications or do not wish to be treated with Peg-IFN, long-term treatment with NAs is the most commonly used treatment strategy.

IFN-BASED THERAPY

Published data have demonstrated that in patients with HBeAg-positive CHB, Peg-IFN achieves a more than 30% HBeAg seroconversion rate after one year of treatment[6]. In a registration trial, Peg-IFN alpha-2a provided a sustained immune control which increased post-therapy; in fact, the HBeAg seroconversion rate continued to increase from 27% at the end of treatment to 32% during the six months after discontinuing treatment, and to 42% 1 year post-treatment[10,11]. Moreover, the seroconversion remained stable over time in > 80% of Peg-IFN alpha-2b treated patients, achieving this end-point at the end of therapy[12]. Peg-IFN also determined HBsAg seroconversion in up to 30% of patients with a long-term follow-up[13].

In patients with HBeAg-negative CHB, Peg-IFN alpha-2a demonstrated a sustained immune control (HBV DNA < 2000 IU/mL) in 31% of patients 1 year post-treatment. Among these, 88% maintained this response up to 5 years follow-up and, remarkably, 28% achieved HBsAg clearance 5 years post-treatment[14].

Peg-IFN treatment remains an attractive therapeutic option since it provides higher rates of off-therapy immune control, including HBsAg clearance, when compared to NAs. However, IFN is effective in only a minority of patients (20%-30%), has a poor tolerability and significant costs. Therefore, the improvement of Peg-IFN efficacy is a major challenge. Several attempts have been made to optimize the cost-effectiveness of IFN-based therapy, including combination therapy, longer treatment duration and identification of pre-treatment and on-treatment predictors of response. *De novo* combination therapy with NAs did not improve sustained response in either HBeAg-positive or HBeAg-negative patients[10,15-17]. Regarding duration of therapy, the NEPTUNE study conducted in patients with HBeAg-positive CHB reported that dose and duration are important because the highest sustained response was obtained with 180 μg and 48 wk compared to 90 μg and 24 wk[18]. Recently, an Italian multicenter study demonstrated in 128 HBeAg-negative patients (mean age 45 years, 94% genotype D, 13% with cirrhosis) that extended treatment with Peg-IFN alpha-2a to 96 wk was well-tolerated and improved the rates of sustained virological response (29% *vs* 12%, $P = 0.03$) in HBeAg-negative genotype D patients when compared to the current standard of care of 48 wk. In addition, 1 year post-treatment, HBsAg clearance (6%) was observed only in the extended therapy group[19]. Among pre-treatment predictors of response, ALT levels, low baseline HBV DNA and virus genotype were significant predictors[6-8]. When combining data from the two largest clinical trials regarding HBeAg-positive CHB patients[9,20], Buster *et al*[13] found that the best candidates for a sustained response to Peg-IFN were genotype A patients with high levels of ALT (ALT ⩾ 2xULN) or low levels of HBV DNA (< 9 $\log_{10}$ copies/mL), and genotypes B and C patients who have both high levels of ALT and low HBV DNA. Genotype D patients have a low chance of sustained response. However, these factors cannot accurately predict response at the individual level; furthermore, ALT and HBV DNA levels are time-dependent and thus their use in clinical practice is difficult.

To obtain additional insight into the individual patient's probability of achieving response to Peg-IFN, the presence of precore and basal core promoter mutants before treatment has been correlated to the serological and virological response in HBeAg-positive CHB patients. Data from this study demonstrated that the presence of a wild-type virus at baseline was an independent predictor of response to Peg-IFN and can assist in improving patient selection for this treatment option[21].

More recently, the role of IL28B polymorphisms, clearly indicated as a baseline host factor predictor of response in patients with chronic hepatitis C, has also been investigated in CHB patients. Studies in HBeAg-positive patients provided conflicting results[22-24]. The only existing data in HBeAg-negative patients are in 101 subjects treated with either conventional IFN or Peg-IFN alpha 2a for 24 mo and followed for 11 years after treatment. Patients with *IL28B rs12979860* genotype CC were shown to have higher EOT (69% *vs* 45%, $P = 0.01$) and higher SVR (31% *vs* 13%, $P = 0.02$) than non-CC patients. Interestingly enough, CC patients had a higher cumulative probability of clearing HBsAg during an observation period of 16 years (38% *vs* 12%, $P = 0.039$)[25]. Further studies are necessary to define the role of *IL28B* polymorphisms as a baseline factor to improve pre-treatment patient selection.

A promising approach to improve the cost-effectiveness of Peg-IFN therapy is a response-guided treatment based on serum HBsAg kinetics which permits early identification of either responders for whom continuation of treatment to week 48 could be beneficial or non-responders who should discontinue IFN treatment.

Two stopping rules at week 12 have been proposed for HBeAg-positive patients: (1) no HBsAg decline; and (2) HBsAg levels > 20000 IU/mL. The negative predictive value (NPV) for a sustained response ranged from 92% to 100% depending on HBV genotypes; thus, HBV genotype-specific stopping-rules may be considered at week 12. However, at week 24, treatment discontinuation is indicated in all patients with HBsAg > 20000 IU/mL, irrespective of HBV genotype[26,27].

In HBeAg-negative genotype D patients, no HBsAg decline and < 2 log copies/mL HBV DNA decline at

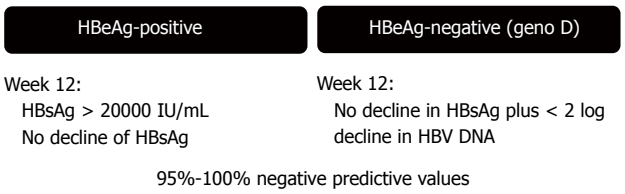

Figure 2 Response-guided therapy using hepatitis B surface antigen levels in pegylated interferon-treated patients: stopping rules[26-29]. HBeAg: Hepatitis B e antigen; HBsAg: Hepatitis B surface antigen.

week 12 has been proposed as a stopping rule and independently validated with a 100% NPV[28,29]. Overall, therapy with Peg-IFN could be discontinued at week 12 in the 20% of primary non-responders, who are therefore candidates for suppressive therapy with NAs (Figure 2).

Recently, it has been demonstrated that, even in HBeAg-negative patients, on-treatment HBsAg kinetics varied according to HBV genotype. In fact, for genotype A, the difference between responders and non-responders was greatest at week 24, while for genotypes B and D, the difference was evident at week 12; there was no significant difference for genotype C over time. Moreover, highly positive predictive values for long-term virological response was obtained by applying end-of-treatment genotype-specific HBsAg level cut-offs[30].

NA-BASED THERAPY

Entecavir and tenofovir are the third-generation NAs recommended as first-line therapy for CHB NA-naïve patients by all international guidelines. In registration trials, both antivirals demonstrated a long-lasting efficacy (viral suppression in more than 95% of patients over 5 years) associated with prevention of developing cirrhosis and, to a greater extent, with fibrosis regression[31-36]. Chang *et al*[31] first documented the histological reversal of cirrhosis in 4 of 10 cases who met the criteria for efficacy analysis while they were in a 3 to 7 year period of virological response to ETV. More robust evidence of cirrhosis reversion has been offered by Marcellin and colleagues who reported the effect of 5 years of viral suppression on histology in liver fibrosis and cirrhosis in 348 patients who had evaluable histology at baseline and at week 240. Of the 96 (28%) patients with cirrhosis (Ishak score $\geqslant$ 5) at baseline, 71 (74%) demonstrated a reduction in fibrosis at year 5 and were no longer cirrhotic[34].

Moreover, registration trials reported a minimal risk of drug resistance (1.2% with ETV and 0% with TDF after 6 years) and a favorable safety profile[31-36]. However, as registration trials are conducted under standardized conditions with strict enrolment criteria in well-selected and compliant patients, long-term efficacy and safety of ETV and TDF are still to be confirmed in real life patients who generally have a more complex clinical profile as they are usually older, with a higher prevalence of cirrhosis and comorbidities treated with several concomitant medications.

Efficacy and safety of entecavir in real life practice

In a retrospective/prospective multicenter Italian study, 418 consecutive NA-naïve patients initiating treatment with ETV 0.5 mg/d were studied. In this cohort, patients were older at baseline (median age 58 years), were predominately infected with HBV genotype D (90%), 49% had cirrhosis, approximately 46% had a body mass index over 25 kg/m^2, and 56% had concomitant diseases. Viral suppression was achieved in 99% of patients over 60 mo of therapy, independent of HBeAg status. Only one patient with a partial virological response at week 48 developed resistance at year 3 of treatment, with a cumulative rate of 0.2%. In HBeAg-positive patients, the 5 year cumulative probability of HBeAg seroconversion and HBsAg loss were 55% and 34%, respectively. HCC developed in six non-cirrhotics with a yearly rate of 0.8%. The 204 compensated cirrhotics remained clinically stable, yet 18 developed a HCC, a 5 year cumulative rate of 13% and a yearly rate of 2.6%, making continuous surveillance for liver cancer mandatory[37].

The single center Hong Kong cohort study prospectively included 222 NA-naïve patients (median age 45 years) who demonstrated a 97.4% 5 year cumulative rate of virological response. Only two cases of resistance (corresponding to a 1.2% cumulative resistance rate up to year 5) were reported in this patient cohort[38].

The European network of excellence for Vigilance against Viral Resistance performed a multicenter cohort study with over 10 European referral centers between 2005 and 2010. The study including 243 consecutive NA-naïve patients receiving ETV monotherapy; the cumulative probability of achieving a virological response at week 144 was 90% in HBeAg-positive patients and 99% in HBeAg-negative patients, and the proportion of HBeAg-positive patients with HBeAg loss was 34%[39]. In this cohort, 81% of patients with partial virological response at 48 wk reached a virological response during prolonged ETV monotherapy and no patient developed ETV resistance. When stratifying patients according to their viral load at week 48, 95% of patients with HBV DNA < 1000 IU/mL and 57% of patients with HBV DNA > 1000 IU/mL achieved a virological response without treatment adaptation during the prolonged treatment period beyond week 48. Therefore, the authors concluded that no treatment adaptation is needed in the majority of NA-naïve patients treated with ETV who reach a partial virological response, particularly in those with HBV DNA < 1000 IU/mL at week 48. In addition, data from the Virgil cohort demonstrated that in cirrhotic patients, virological response to ETV is associated with a lower probability of developing a clinical event and disease progression[40].

The safety profile of ETV in real life studies has been largely consistent with those of registration trials as there have been no reports of serious drug-related side effects, discontinuation or renal toxicity[37-41]. One retrospective study identified five cases of lactic acidosis among 16 ETV-treated patients with decompensated liver disease.

Table 3 Cross-resistance data for the most frequent resistant hepatitis B virus variants[43]

HBV variant	LVD	LdT	ETV	ADV	TDF
Wild-type	S	S	S	S	S
M204I/V	R	R	I	S	S
L180M + M204V	R	R	I	S	S
A181T/V	R	R	S	R	I
N236T	S	S	S	R	I
A181T/V + N236T	R	R	S	R	R
L180M + M204V/I ± I179T ± T184G ± S202I/G ± M250I/V	R	R	R	S	S

HBV: Hepatitis B virus; LVD: Lamivudine; LdT: Telbivudine; ETV: Entecavir; ADV: Adefovir; TDF: Tenofovir; S: Sensitive; I: Intermediate/reduced susceptibility; R: Resistant.

These patients all had highly impaired liver function, with model for end-stage liver disease scores of 22 or higher[42]. In two subsequent studies enrolling patients with hepatic decompensation, no cases of lactic acidosis were reported[43,44].

Efficacy of tenofovir in real life practice

In the multicenter European cohort study, 374 consecutive NA-naïve patients receiving tenofovir (245 mg/d) were retrospectively and prospectively followed for a median period of 39 mo. At baseline, median age was 55 years, 35% of patients had cirrhosis, and concomitant diseases were present in 47%[45]. Virological response rates increased over time, reaching 97% at year 4, independent of HBeAg status. Virological breakthrough was reported in 2% of patients, with no potential resistance-associated mutations identified to date. In HBeAg-positive patients, cumulative probability of HBeAg seroconversion at 4 years was 37%. Sixteen patients (17%) cleared HBsAg (11 HBeAg-positive patients), six of whom successfully interrupted tenofovir. Most partial virological responders at week 48 achieved undetectable HBV DNA during additional treatment. Serum creatinine and phosphorus median levels remained unchanged over time. The proportion of patients with an eGFR of < 50 mL/min (as calculated by the Modification of Diet in Renal Disease formula) increased from 2% to 3% (year 4). The TDF dose was reduced in 19 patients (5%) because of a decline in the estimated glomerular filtration rate in 17 and low serum phosphate levels in two. Therapy was discontinued in seven patients (2%) who were switched to ETV. Nine additional patients withdrew from TDF and switched to ETV because of non-renal-related side effects. HCC developed in 10 compensated cirrhotics (4 year cumulative probability: 17%, 4.2%/year) and in six non-cirrhotics (4 year cumulative probability: 4%, 1%/year), while no cirrhotics clinically decompensated[45].

Management of antiviral drug resistance

The management of treatment failure has changed significantly in recent years due to the availability of potent antivirals. An appropriate rescue therapy should be initiated with the most effective antiviral drug without cross-resistance to reduce the risk of selecting multiple drug-resistant viral strains (Table 3)[46]. In the past years, the add-on strategy was the therapeutic approach recommended by guidelines in order to prevent the emergence of multi-drug resistant strains and raising the resistance barrier. However, with the availability of more potent drugs, such as entecavir and tenofovir, there is a trend to recommend a switch to a complementary drug with a high barrier to resistance. Both options are considered in the recent EASL guidelines (Table 4)[6]. The switch strategy does not apply to patients who have been exposed to multiple monotherapies; these patients should be treated with add-on strategies in order to minimize the risk of subsequent treatment failure.

NA treatment discontinuation

In HBeAg-positive patients with documented HBeAg seroconversion, NA-treatment can be discontinued after 6-12 mo consolidation therapy[6-8], although the optimal duration of consolidation treatment is not clearly defined. However, the long-term durability of HBeAg seroconversion induced by NAs is controversial and high relapse rates have been reported, suggesting that long-term continuation of NA-treatment, irrespective of the occurrence of HBeAg seroconversion, appears to be necessary[47].

Overall, the ideal end-point for stopping NA-treatment is HBsAg loss; however, the likelihood of HBsAg clearance is very low in clinical practice[6-8]. Studies are underway to determine if it is possible to successfully combine the potent effects of NAs with Peg-IFN to increase the HBsAg clearance rates and allow more patients to stop therapy. Recent reports propose quantification of serum HBsAg levels together with serum HBV DNA levels for predicting the outcome after treatment discontinuation in individual patients and thus whether therapy can be safely stopped. Petersen and colleagues showed that stopping long-term NA-therapy in HBeAg-negative CHB patients without advanced liver disease might be an option for patients with HBsAg titers < 500 IU/mL since these selected patients developed a high rate of HBsAg loss off-therapy.

CONCLUSION

Chronic hepatitis B remains a serious clinical problem because of its worldwide distribution and potential adverse sequelae. Over the last decades, treatment of CHB has greatly advanced due to the availability of safe and effective drugs and new standards of care and guidelines have been developed. Both Peg-IFN and two NAs, entecavir and tenofovir, can currently be prescribed as first-line monotherapy for CHB.

Peg-IFN treatment is the only short-term treatment strategy which provides significant off-treatment sustained responses, including loss of HBsAg. However, as Peg-IFN is effective in 20%-30% of patients, it should

Table 4 European Association for the Study of the Liver 2012 Guidelines recommendations in resistant patients[6]

Resistance	Action
LAM resistance	Switch to TDF (add ADV if TDF not available)
ADV resistance	If patient was NA naive before ADV: switch to ETV or TDF; ETV may be preferred in such patients with high viremia If patient had prior LAM resistance: switch to TDF and add a nucleoside analogue
LdT resistance	Switch to or add TDF (add ADV if TDF not available)
ETV resistance	Switch to or add TDF (add ADV if TDF not available)
TDF resistance	TDF resistance not detected to date: add a nucleoside analogue Switch to ETV if patient had no prior LAM resistance or add ETV in patients with LAM resistance

LAM: Lamivudine; ADV: Adefovir dipivoxil; TDF: Tenofovir; LdT: Telbivudine; ETV: Entecavir.

be considered only for patients with an elevated possibility of response based on pre-treatment and on-treatment factors. In particular, quantitative serum HBV-DNA and HBsAg levels may be suitable to identify patients early who are unlikely to benefit from Peg-IFN early during the treatment course, thereby avoiding unnecessary therapy. Nevertheless, despite this individualized and response-guided approach, increasing the cost-effectiveness of Peg-IFN therapy remains a clinical challenge. Combining Peg-IFN with NAs appears to be the most appealing approach to increase the efficacy of antiviral therapy and new trials on a combination of Peg-IFN with ETV or TDF are required.

Currently, NAs represent the treatment option most often used in the majority of CHB patients. TDF and ETV suppress HBV replication in most treatment-naïve field practice patients with CHB but fail to prevent HCC development, independent of liver disease severity. NA long-term administration raises several concerns: the patient's commitment to lifelong treatment, adherence, long-term safety, drug resistance in the long-term and costs. Different strategies combining Peg-IFN with ETV or TDF might achieve an antiviral synergy and provide new opportunities to increase HBsAg clearance rates and shorten treatment duration.

Finally, development of new antiviral agents targeting other steps in the HBV replication cycle (viral entry, capsid assembly, viral RNA transcription and epigenetic control of cccDNA) and new immune therapies restoring immune response to HBV remain a major research challenge to improve the efficacy of current antiviral therapy and to achieve HBsAg loss and HBV eradication.

ACKNOWLEDGMENTS

The authors are grateful to Ms. Paulene Butts for her assistance in the preparation of the manuscript.

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P- Reviewers: Gong ZJ, Faintuch J **S- Editor**: Gou SX
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DOI: 10.4254/wjh.v6.i5.293

World J Hepatol 2014 May 27; 6(5): 293-305
ISSN 1948-5182 (online)

REVIEW

Cystic echinococcosis of the liver: A primer for hepatologists

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Received: November 12, 2013 Revised: January 22, 2014
Accepted: March 17, 2014
Published online: May 27, 2014

Abstract

Cystic echinococcosis (CE) is a complex, chronic and neglected disease with a worldwide distribution. The liver is the most frequent location of parasitic cysts. In humans, its clinical spectrum ranges from asymptomatic infection to severe, potentially fatal disease. Four approaches exist in the clinical management of CE: surgery, percutaneous techniques and drug treatment for active cysts, and the "watch and wait" approach for inactive cysts. Allocation of patients to these treatments should be based on cyst stage, size and location, available clinical expertise, and comorbidities. However, clinical decision algorithms, efficacy, relapse rates, and costs have never been properly evaluated. This paper reviews recent advances in classification and diagnosis and the currently available evidence for clinical decision-making in cystic echinococcosis of the liver.

Key words: Cystic echinococcosis; Hydatidosis; Clinical management; Diagnosis; Treatment; Surgery; Albendazole; Watch-and-wait; Follow-up; Percutaneous treatment

Core tip: Cystic echinococcosis (CE) is a neglected parasitic disease and echinococcal cysts are mostly located in the liver. Therefore, CE should always be included in the differential diagnosis of cystic lesions of the liver. However, diagnosis and clinical management can be difficult because of the combination of clinical variables (cysts stage, size, presence of complications, available expertise and three different treatments that have never been systematically compared). This review summarizes current knowledge and open issues in this field for those hepatologists who have limited or no experience with this complex condition.

Rinaldi F, Brunetti E, Neumayr A, Maestri M, Goblirsch S, Tamarozzi F. Cystic echinococcosis of the liver: A primer for hepatologists. *World J Hepatol* 2014; 6(5): 293-305 Available from: URL: http://www.wjgnet.com/1948-5182/full/v6/i5/293.htm DOI: http://dx.doi.org/10.4254/wjh.v6.i5.293

INTRODUCTION

Hepatologists may encounter cystic echinococcosis (CE) in their practice. However, due to its relatively low prevalence in many Western countries, this infection is poorly characterized and its complex management can be difficult for clinicians unfamiliar with this condition. Moreover, hepatic CE should be included in the differential diagnosis of focal liver lesions. In this paper, we summarize the current knowledge on clinical management of hepatic CE to increase hepatologists' awareness of this complex condition.

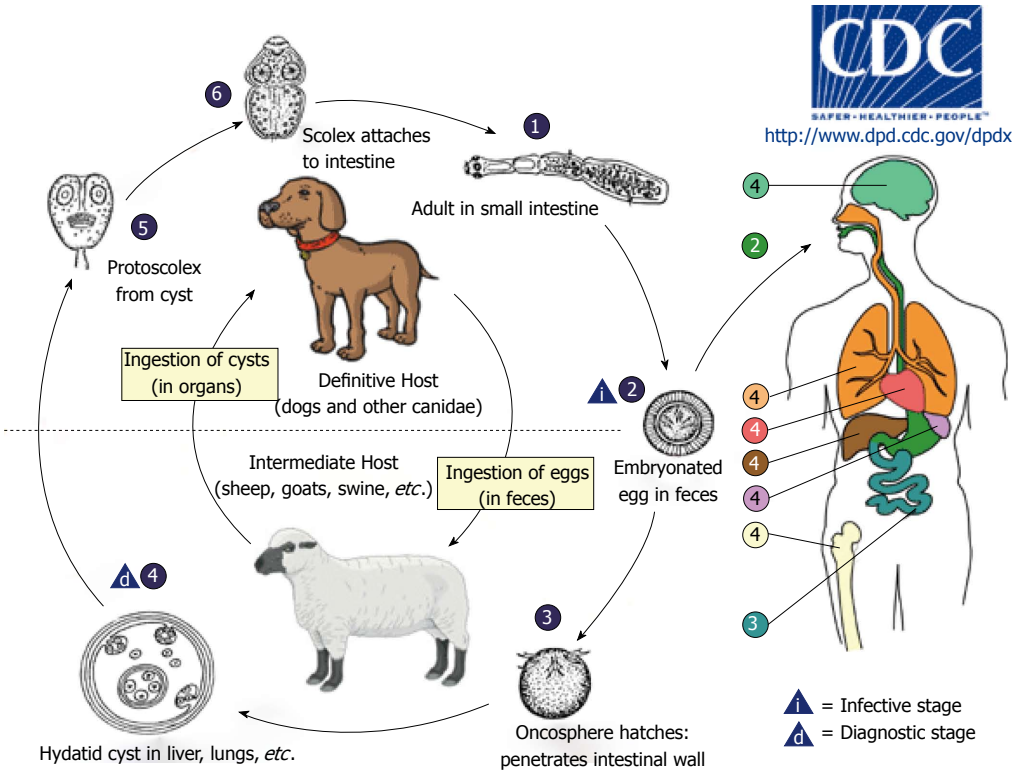

Figure 1 Life cycle of *Echinococcus granulosus*. Source: www.cdc.gov.

CE, or hydatidosis, is caused by the larval stage (metacestode) of *Echinococcus granulosus* (*E. granulosus*). Its life cycle develops in dogs and other canids, which harbor the adult tapeworm in the intestine, and herbivores (or humans as dead-end occasional host) as intermediate hosts, where the larval metacestode form develops in different organs (Figure 1).

Once eggs are ingested by the intermediate host, the oncosphere (also named exacanth larva), is released from the keratinized embryophore in the stomach and intestine where it penetrates the small intestine wall *via* its hook movements. The oncosphere is then carried *via* portal flow to the liver and other organs where the metacestode implants. Organs may also be reached through the lymphatic system[1]. This process results in primary echinococcosis, while secondary echinococcosis follows the spillage of protoscoleces (tapeworm heads) or small daughter cysts from the original cyst that ruptures following trauma or surgery and their seeding, primarily in the peritoneum for abdominal cysts[2].

The impact of CE on human health is significant, with an estimated 1.2 million people affected and 3.6 million DALYs (Disability Adjusted Life Years) lost globally[3]. Despite the low mortality rate (0.2/100000 population with a case fatality rate of 2.2%) morbidity is high[4]. Moreover, it has a major economic impact with an estimated annual livestock production loss of up to 2190 million US$[5].

Despite these figures, the infection is still under-reported and has received to date much less attention than infections of comparing burden[5]. In humans, its clinical manifestations range from asymptomatic infection to severe, potentially fatal disease.

The liver is the most frequent location of echinococcal cysts, representing approximately 70% of cases[4]. The lungs are the second most common location; however, CE can present in virtually any other organ, although this rarely occurs[1,2].

Echinococcal cysts consist of a periparasitic host tissue (pericyst or adventitia), which surrounds the larval endocyst, and an endocyst itself. The endocyst is composed of an outer, acellular laminated layer and an inner layer, the germinal layer, which gives rise, in fertile cysts, to brood capsules and protoscoleces[6]. Each protoscolex may develop into an adult tapeworm if ingested by a suitable definitive host. The cyst is filled with clear fluid containing molecules of both parasite and host origin, numerous brood capsules, and protoscoleces. Some cysts may also harbor daughter cysts of variable size (Figure 2). The fluid is clear in the early stages (Figure 3A), but can be yellowish and turbid, with fragments of endocyst in advanced stages (*e.g.*, in CE3b cysts) or after months of treatment with albendazole (Figure 3B).

E. granulosus occurs in a broad range of geographic areas and can be found on all continents except Antarctica, and in circumpolar, temperate, subtropical, and tropical zones. Eurasia, Africa, Australia, and South America show the highest prevalence[7]. Within endemic zones, the prevalence varies from sporadic to high, with recent studies showing an higher prevalence among females and with increasing age[8]. Only a few countries can be regarded as free of *E. granulosus* infection[3].

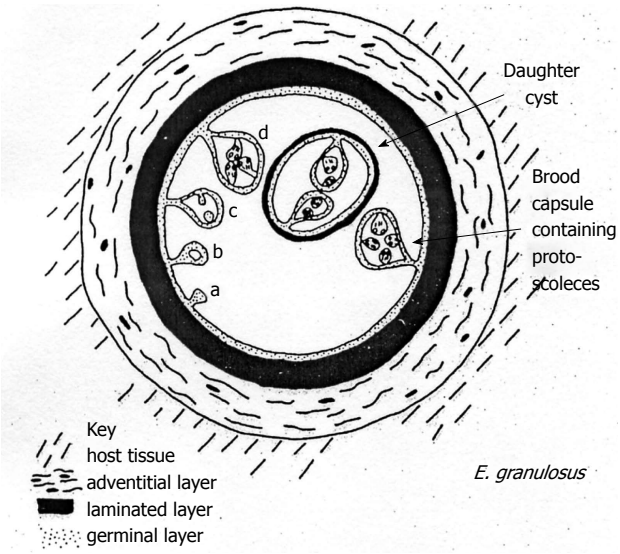

Figure 2 Diagrammatic representation of the metacestode of *Echinococcus granulosus*. Source: Eckert J, Gemmell MA, Meslin FX and Pawłowski ZS. WHO/OIE Manual on Echinococcosis in Humans and Animals: a Public Health Problem of Global Concern. Paris, France, 2001. *E. granulosus*: *Echinococcus granulosus*.

E. granulosus parasites from different hosts show considerable phenotypic variation in terms of morphology, larval growth *in vivo* and *in vitro*, range of host infectivity, and biochemical features. Currently, 10 genotypic strains of *E. granulosus* have been identified (G1-G10), and the impact of these variations on CE epidemiology, pathology and control is being investigated. Genotypes are grouped into 4 species that constitute the *E. granulosus* complex: *E. Granulosus sensu strictu* (G1-G3), *E. equinus* (G4), *E. ortleppi* (G5) and *E. canadensis* (G6-G10). The great majority of *E. granulosus* isolates from humans thus far characterized have been of the sheep genotype (G1)[1,2].

COURSE OF INFECTION

Acute infection in humans has never been documented[9], thus all available data come from experimental studies in animal intermediate hosts. Cavity formation and the development of both germinal and laminated layers of the cyst wall occur 10 to 14 d post infection in the mouse model[10]. Formation of brood capsules and protoscoleces requires a longer time period in sheep, from 10 mo to 4 years[11].

Based on clinical observations using ultrasound (US), the cysts progress from a fluid-filled unilocular cavity to a pseudo-solid, eventually calcified lesion. The sequence of cyst development between these 2 stages is poorly understood[12]. Long-term clinical observation indicates that the early stages are CE1 and CE3a cysts, while final stages are represented by CE4 and CE5, referring to the standardized US classification (see "Imaging" below)[13]. Preliminary observations suggest that cysts that have reached the CE4 stage as a result of treatment may revert to CE3b more often than those reaching the inactive stage spontaneously; this may occur many years after apparently successful treatment[14] (Junghanss, personal communication). The origin and fate of CE2 and CE3b stages are less clear. CE2 may represent a relapsed CE3a, and CE3b a relapsed CE4, but long-term observations of large cohorts of patients are needed to confirm this hypothesis.

Figure 3 Appearance of cystic fluid. A: Clean and clear cyst fluid from a diagnostic puncture; B: Yellowish and turbid echinococcal fluid in a catheter bag after percutaneous catheterization.

The growth rate of cysts is variable. The average increase in cyst diameter is thought to be 1 cm/year, but data on the natural history of CE are scarce. Cysts may behave differently in different subjects and their growth rate also depends on the surrounding host tissue, with growth rates up to 5 cm/year reported for brain cysts[15-19].

DIAGNOSIS

The presentation of human CE is protean. Patients come to the clinician's attention for a variety of reasons. Potential presentations may be due to the mechanical effect of a large cyst on surrounding tissues, rupture of a cyst causing an acute hypersensitivity reaction, or complications such as biliary obstruction or embolism. The cyst is often asymptomatic and diagnosed accidentally during radiographic examination, surgery, or during evaluation of other clinical diagnoses.

Common symptoms are upper abdominal discomfort and pain and poor appetite. Physical findings are hepatomegaly, presence of an abdominal palpable mass and abdominal distension. Cysts in the liver should be included in the differential diagnosis of several conditions, such as jaundice, colicky pain, portal hypertension, ascites, compression of the inferior vena cava and Budd-Chiari syndrome and can be misdiagnosed as non-parasitic cysts, single or multiple hemangiomas, pyogenic or amebic liver abscess, hematoma, adenoma, adenocarcinoma, hepatocellular carcinoma, metastases, focal or diffuse lymphoma, alveolar echinococcosis, and textiloma[20,21].

As the infection may remain silent for years before the enlarging cysts cause symptoms, the clinical diagnosis of CE is often difficult and requires a combination of physical examination, imaging techniques, in particular

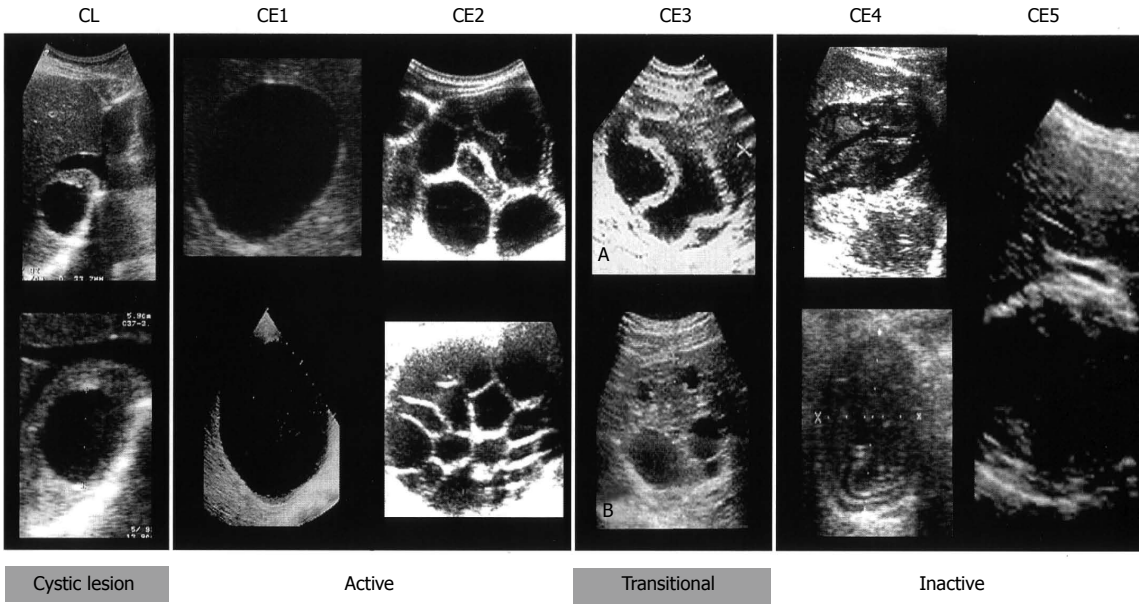

Figure 4 World Health Organization Informal Working Group on Echinococcosis standardised classification of echinococcal cysts. Source: World Health Organization Informal Working Group on Echinococcosis. CE: Cystic echinococcosis; CL: Cystic lesions.

US, and serology; the latter plays a supportive role in diagnosing CE despite the development of sensitive serodiagnostic tests and the use of different antigen sources.

Imaging

Imaging techniques have revolutionized the diagnosis and clinical management of CE. Gharbi *et al*[22] developed the first US classification for CE in 1981. Other classifications were subsequently produced but were not widely adopted. In 1995, the WHO Informal Working Group developed an international standardized US classification that could be universally applied to replace the plethora of classifications in use.

This classification, published in 2003[23], differs from Gharbi original classification by introducing a cystic lesion (CL) category to include cysts of unclear origin, and by reversing the order of CE types 2 and 3 (Figure 4). The number of cyst types remains unchanged from Gharbi's classification and the types are categorized into active, transitional, and inactive stages. CL cysts are not included as a type of CE, as they require further evaluation before being classified as CE[24]. CE1 and 2 are active, usually fertile cysts containing viable protoscoleces. CE3 are cysts entering a transitional stage where the integrity of the cyst has been compromised either by the host or by chemotherapy. CE4 and CE5 are inactive cysts that have lost their fertility and are degenerating. A more recent amendment to the WHO classification clarifies that calcifications are not limited to CE5 cysts, but may be present to a various extent in all cystic stages and are therefore not indicative of cyst death[25].

Data on long-term follow-up of cysts treated with albendazole and percutaneous treatment provide ground for a further sub-classification of CE3 (transitional) cysts into CE3a (with detached endocyst) and CE3b (predominantly solid with daughter vesicles). This has important implications for clinical decision-making and prognosis[26]. The sub-classification of CE3 into CE3a and CE3b is supported a recent work using high-field ^{1}H magnetic resonance spectroscopy evaluating the metabolic profile of cysts contents *ex vivo*[27]. This study confirmed findings from optical microscopy that CE3a are equally likely to be viable or non-viable, whereas CE3b are consistently viable. Of note, CE3a and CE3b also respond differently to non-surgical treatments[28,29]. In light of these features, CE3b cysts should be considered as active, while CE3a are the transitional cysts *sensu stricto*.

The same study confirmed the biological activity of CE1 and CE2 and the inactivity of CE4 and CE5. Another study showed how a CE1 brain cyst, in *in vivo* magnetic resonance spectroscopy matched the profile of an active stage before the medical treatment with albendazole (ABZ) and that of an inactive one after ABZ[30]. CE2 and CE3b cysts tend to relapse both after PAIR (puncture, aspiration, injection of a scolecidal agent, and reaspiration) and ABZ[26,28,29], and several studies suggest that a strong Th2 response correlates with susceptibility to disease (active cyst), whereas a Th1 response correlates with protective immunity (inactive cyst), however this is not clear cut[31-36].

Computed tomography (CT), including spiral or multidetector CT, with multiplanar reformations, and magnetic resonance imaging (MRI), with at least a T2-weighted imaging sequence, and if necessary cholangiopancreatography, have distinct indications: (1) impaired US visualization due to obesity or subdiaphragmatic location of the cyst; (2) disseminated disease; (3) extra-abdominal location; (4) complications (cyst infection, cysto-biliary fistulae); and (5) pre-surgical evaluation and follow-up (Figure 5). Whenever possible, MRI is pre-

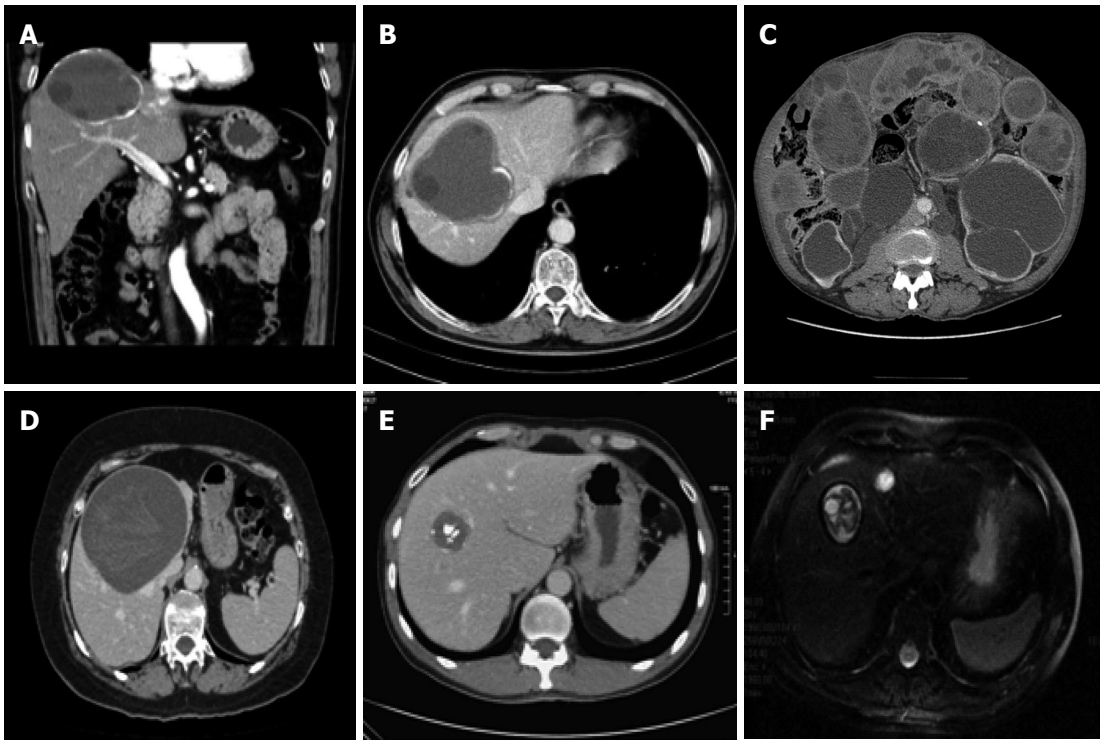

Figure 5 Computed tomography and magnetic resonance imaging of hepatic cystic echinococcosis. A and B: Contrast enhanced computed tomography (CT) abdominal scan of a 59-year-old male patient with a CE3b cyst in the Ⅶ liver segment; C: Disseminated peritoneal echinococcosis in 64-year-old male patient, 30 years after surgery for CE without albendazole prophylaxis[1]; D: Abdominal CT scan of a 59-year-old female patient with a CE3a cyst in the Ⅳ-Ⅷ liver segments; E: Abdominal CT scan of a 47-year-old male patient with a CE5 calcified cyst in the Ⅷ liver segment; F: Abdominal magnetic resonance imaging scan of a 52-year-old male patient with a CE3b cyst in the Ⅷ segment.

ferred to CT for pre-treatment assessment[37,38].

Serology

Routine blood tests are not specific for CE, and with liver involvement they can be normal or suggestive of cholestasis with or without hyperbilirubinaemia or raised transaminases or γ-glutamyltransferase (γ-GT)[1,39,40]. Transient elevation of γ-GT and alkaline phosphatase, in association with hyper-transaminasemia and eosinophilia, may indicate cyst rupture in the biliary tree. Despite CE being a helminthic infection, eosinophilia is usually moderate or absent.

Despite the development of sensitive laboratory tests and the use of different antigen sources, serology remains complementary to imaging in the diagnosis of CE. Currently, lipoprotein antigen B (AgB) and Ag5, the major components of cystic fluid, have received the most attention with regard to diagnosis, but purified cyst hydatid fluid is still the most widely used in current assays for immunodiagnosis of CE, which are not standardized[41,42]. In clinical practice, usually two tests are performed (for example ELISA and indirect hemagglutination (IHA), with immunoblotting (IB) as a confirmatory test. IHA and ELISA show sensitivity for hepatic cysts ranging between 85% and 98%[42-46]. The result of a single test is not considered diagnostic, and the two tests are generally run in parallel. IB is performed as a confirmatory test when ELISA and IHA are inconclusive or for the differential diagnosis with other infections, although *E. granulosus* specific bands may be also be detected in the serum of patients affected by *E. multilocularis* and rarely *T. solium* cysticercosis[47]. False positives result from cross-reactivity, most commonly with other cestode infections (*E. multilocularis, Taenia solium* cysticercosis) and some other parasitoses (schistosomiasis, liver flukes, filariasis), but also from non-infectious diseases such as malignancies and cirrhosis[1,41,48-50].

Serologic testing for CE is hampered by many problems[41-43,45]. These include low sensitivity, partially dependent upon the location of the cysts in the body and the cystic stage, and the inability of serology to clearly distinguish between active and inactive cysts when US is inconclusive[43]. Up to 20% of patients with single hepatic cysts and up to 50% of those with lung cysts may be seronegative at diagnosis, while patients with cysts in other locations are often seronegative. In addition, patients with multiple cysts are generally seropositive. In the case of hepatic cysts, patients with CE1 and CE4-CE5 cysts are often seronegative (30%-58% and 50%-87% respectively), while rates of negativity are lower in the presence of CE2 and CE3 cysts (5%-20%). It is also worth noting that serodiagnostic tests may be persistently positive for > 10 years even after radical surgical removal of the cysts, and are often positive in the presence of inactive cysts[17,51,52]. This may lead inexperienced clinicians to prescribe unnecessary treatment and cause unjustified anxiety to the patient. New antigens are under investigation which promise to have higher diagnostic performances in

these situations[53].

Microscopical examination

When US and serology are inconclusive, a direct analysis of the material obtained by percutaneous aspiration is needed. The procedure must be performed with the assistance of an anesthesiologist because of the very low but nonetheless present risk of anaphylaxis[54]. The presence of protoscoleces or their components or of antigens specific to *E. granulosus* indicates the parasitic nature of the cyst[55].

TREATMENT

There is no standard treatment for hepatic CE. The appropriate treatment depends on individual patient factors, cyst characteristics, the therapeutic resources available, and the physician's preference[56]. Matters are further complicated by the dearth of randomized clinical trials evaluating treatment options, and the ensuing low level of evidence to support one therapeutic modality over another[57,58] .

Surgery has long been considered the best, if not the only, option in the treatment of CE. However, in the past two decades, medical treatment, percutaneous procedures, and a "watch and wait" approach have been successfully introduced and have replaced surgery as the treatment of choice in selected cases[59].

Surgery

While surgery is increasingly being replaced by other options in uncomplicated cysts, it maintains a central role in complicated cysts (*i.e.*, rupture, biliary fistula, compression of vital structures, superinfection, hemorrhage), cysts at high risk of rupture, or large cysts with many daughter vesicles that are not suitable for percutaneous treatments.

Surgery can be performed as an open procedure, with either radical or conservative techniques, or laparoscopically. There are still controversies as to the safest and most effective technique, and in which cases it should be applied[57,60,61]. As a rule, perioperative ABZ prophylaxis, from 1 wk prior to surgery until 4 wk postoperatively, is necessary to minimize the risk of secondary echinococcosis from seeding of protoscoleces in the abdominal cavity[59].

Radical surgery aims to remove the entire pericystic membrane and the parasitic contents with or without hepatic resection, and can be performed with either the "open-cyst" or "closed-cyst" method. In conservative procedures, only the parasitic material is removed while part or all of the pericyst is left in place and the residual cavity is managed with different techniques, such as omentoplasty, capitonnage, or external drainage.

A cleavage plan between the inner layer of the host's reaction towards the parasite and the cyst outer layer, or "adventitia", as described by Peng *et al*[62], limits damage to liver parenchyma when dissecting around the cyst and allows for safer removal. Based on these anatomical considerations, such an operation should be more adequately termed "total cystectomy." Mortality ranges between 0.8% and 6.5%, morbidity between 12% and 84%, and relapse rate between 2% and 30%[39,60,63,64].

It is commonly perceived that the more radical the surgery, the higher the operative risk but the lower the risk of relapses and *vice versa*. However, results of meta-analyses and single center studies indicate that radical surgery is superior to conservative surgery, with lower morbidity (3%-24% *vs* 11%-25%), mortality (1%-1.8% *vs* 2%-5%) and recurrence rates (2%-6.4% *vs* 10.4%-40%)[61,64-66], although the type of surgery was not found to be a predictive factor of post-surgery complications in the study of El Malki *et al*[60]. Other factors associated with surgical outcome are large cyst size, more than 3 hepatic cysts, presence of biliary fistulae, age > 40 years, repeated surgery due to recurrence, capitonnage alone as a measure of residual cavity management, and cyst rupture during surgery[60,61,64,67,68].

Recurrence, both local and as secondary echinococcosis, is associated with spillage during removal of the cyst, incomplete removal of the endocyst, and possibly the presence of unnoticed exophytic cyst development[63,69]. For the latter, intraoperative US has been shown to be an important tool to improve the quality of hepatic surgery[70].

Infection and biliary communication with the cyst (*i.e.*, leakage or rupture with cholestasis) are the most common complications of echinococcal cysts and can occur before or after surgical or percutaneous interventions[71,72]. Cyst diameter is a factor associated with a high risk of biliary-cyst communication in clinically asymptomatic patients. A recent study reported that cyst diameter > 7.5 cm had a specificity and sensitivity for biliary-cyst communication of 73% and 79%, respectively[73]. Thus, surgeons operating on cysts larger than 7.5 cm should be prepared to deal with this complication and should perform preoperative retrograde cholangiopancreatography or MR imaging[73,74].

Several methods have been proposed for the management of cyst-biliary communications. When intrabiliary rupture is diagnosed pre- or intra-operatively, a simple suture of the orifice is sufficient if there are no cystic contents in the biliary tree and the common bile duct has a normal caliber. When cyst contents are found in the biliary tree or the common bile duct has an abnormal caliber, evacuation of the cystic content and a T-tube drainage placement or even a coledochoduodenostomy are needed[71,75]. Alternatively, endoscopic treatment with sphincterotomy and placement of a nasobiliary catheter has been performed[76,77]. Postoperative bile leakage resulting in symptomatic bilomas or high-output biliary fistulae can be managed endoscopically by sphincterotomy with nasobiliary drainage or biliary stenting[78,79].

Surgical interventions other than segmentectomies can result in a number of residual cavities that may be mistaken for recurrences or other conditions[20]. Some groups have evaluated these findings and attempted to

categorize them relative to the type of surgical procedure performed[80].

A recent review on management of post-surgical complications concluded that " the evidence level is low" and that "there are many questions and few answers"[81].

Percutaneous treatments

Percutaneous treatments for abdominal CE were introduced in the mid-1980s, with the adoption of minimally invasive procedures made possible by new imaging tools, particularly CT and US[82-85]. These treatment modalities aim either to destroy the germinal layer with scolecidal agents or to evacuate the entire endocyst.

The most popular method is PAIR[13]. Several modified catheterization techniques are used to evacuate the endocyst, and are generally reserved for cysts which are difficult to drain or tend to relapse after PAIR, such as multivesiculated cysts or cysts with predominantly solid content and daughter cysts[26].

Catheterization techniques are based on the aspiration of the "solid" content of the cyst, the endocyst surrounded by pseudocaseous inflammatory material, through a large-bore catheter or other device. Several variants of these techniques have been proposed, in particular percutaneous evacuation (PEVAC)[86], a modified catheterization technique[87], and dilatable multi-function trocar[88].

Puncture of echinococcal cysts has long been discouraged because of the risk of anaphylactic shock and spillage of the fluid; however, as experience with US-guided interventional techniques has increased since the early 1980s, a growing number of articles have reported its safety in treating abdominal, especially liver, echinococcal cysts. In a recent systematic analysis on percutaneous aspiration of echinococcal cysts, only 2 cases of lethal anaphylaxis (0.04%) and 99 reversible anaphylactic reactions (1.8%) were reported[54]. This study divided the complications related to cyst puncture into major (0.5% of cases with anaphylactic shock and peritoneal liquid seeding, liver or intra-abdominal abscess, sepsis, biliary fistulas) and minor (10%-30% of patients with fever, hypotensive reactions, nausea, vomiting, skin rash, respiratory symptoms). Peritoneal seeding has never been reported, but it is difficult to assess the true rate because many reported series have a short follow-up time. Prophylactic administration of ABZ starting 4 h before the puncture and for at least 30 d after puncture is a cautionary measure that should always accompany PAIR[59].

PAIR is performed with several variants of the standard protocol and is generally successful at inducing permanent solidification of medium-sized CE1 and CE3a cysts[13]. A few reports with long-term follow-up indicate that multivesiculated cysts (*i.e.*, CE2 and CE3b) tend to relapse repeatedly after PAIR[26,29,89,90]. Reported morbidity and mortality range from 8.5%-32% and 0%-1% respectively[89,91-94]. Mean hospital stay is 1-4 d compared to 12 d in case of surgery[89,91,93]. PAIR has also been performed in remote, resource-poor areas using portable US machines[95]. Overall response rates range from 72%-97%, with relapse rates from 1.6%-5%[89,91,92,94,96]. However, these figures vary greatly when cyst stages are taken into account. Indeed, unilocular CE1 and CE3a cysts respond very well to percutaneous treatment (> 80% response), while multi-vesiculated CE2 and CE3b cysts have a success rate lower than 40%[29,89,90]. Giant CE1 and CE3a cysts of 10 cm or greater, should preferably be treated with a large catheter left in place until the daily drainage is less than 10 mL, on average 3 wk[97].

The experience with catheterization techniques in CE2 and CE3b cysts is more recent and less extensive than that with PAIR, and results from series with long-term follow-up are needed before their efficacy can be determined. Data available for PEVAC in cysts with cysto-biliary fistulas are less than satisfying, given the long hospitalization and catheter times, up to 128 and 55 d, respectively[86]; in these cases PEVAC does not compare favorably with surgery.

The use of percutaneous techniques should be reserved for referral or specialized centers where teams are prepared to deal with possible complications and an anesthesiologist should always be present during the procedure.

Use of scolecidal agents in surgery and percutaneous treatments: Scolecidal agents should be applied only after having excluded the presence of cysto-biliary fistulae, either with intraoperative cystoscopy or evaluating bilirubin content in the cyst fluid. Although chemical sclerosing cholangitis, due to contact of the scolecidal agent with the biliary ducts, has never been reported using PAIR, several reports are present in the literature after surgery[98-100] and damage to the biliary epithelium has been shown in animal models[101,102]. While hypertonic (15%-20%) saline and 95% ethanol are the most widely used scolecidal agents for percutaneous treatments, a range of other compounds have been tested or are being investigated in the attempt to find an agent that does not damage the biliary epithelium[103-106].

Direct intracystic injection of mebendazole (MBZ) has been successfully performed in animals and humans, and ABZ sulfoxide, the active metabolite of ABZ, has been successfully injected in cysts in animals, but not in humans[107-110]. However, little difference has been found in *in vitro* studies between the effect of hypertonic saline and that of ABZ sulfoxide or sulfone[103]. Unfortunately, ABZ sulfoxide is not available as an injectable formulation and this prevents its clinical use.

Chemotherapy

The use of benzimidazole (BZD) carbamates in the treatment of CE was introduced in the 1970s. While both albendazole and MBZ have been proven effective against the larval stage of *E. granulosus*, ABZ is the current treatment of choice due to better absorption[111]. ABZ is administered orally at a dose of 10-15 mg/kg per day generally for 3-6 mo; administration should be continu-

ous without treatment interruptions, in contrast to the recommendation in the 1980s[26,112]. However, the optimal dose and duration of treatment with ABZ have not been formally assessed.

The comparative rarity of CE in many industrialized countries where BZD is available and affordable is such that only a few centers are able to follow sufficient numbers of patients within a reasonable period of time. Thus, most studies are small, and few have adequate controls.

In the largest series published thus far, 848 patients with 929 cysts received 3-6-mo continuous cycles of MBZ or ABZ treatment[113]. Long-term follow-up showed that 74.1% of the cysts developed degenerative changes. These were more frequent in ABZ-treated than in MBZ-treated cysts (82.2% *vs* 56.1%; $P < 0.001$). During follow-up, 104 cysts (22%) had degenerative changes, whereas 163 cysts (25%) relapsed. In other series, reported outcome rates for hepatic cysts are: 28.5%-58% cure/marked improvement, 10%-51% partial response, 13%-37% no change, and 4%-33% worsened[112,114-120]. Relapse rates range from 9%-25%[112,113,116,121], and, although responsive to subsequent treatments, cysts tend to relapse multiple times[28]. Factors associated with treatment outcome include cyst stage, size, and localization. Unilocular (CE1 and CE3a) cysts and small cysts (< 6 cm) respond better and faster to ABZ treatment compared with multivesciculated (CE2 and CE3b) and larger cysts, with a lower relapse rate[28,113,117,120,122], as clearly shown in the systematic review by Stojkovic *et al*[28]. A recent study highlighted the importance of at least 12 mo of follow-up, since it is difficult to predict cyst behavior after treatment[28].

Adverse effects of BMZ include headache (10% of cases), gastrointestinal symptoms (56%), hepatotoxicity, severe leukopenia, neutropenia or thrombocytopenia (< 1%), and alopecia (2%)[59,123]. Increases in aminotransferases (15% cases) may be due to drug-related efficacy or to real drug-related toxicity. Risks observed in laboratory animals include embryotoxicity and teratogenicity. While teratogenicity is theoretical, it is nonetheless good practice to avoid use during pregnancy whenever possible. Thus, the treatment should be delayed until after delivery[124]. Hospitalization is not necessary, but regular follow-up is required with a monthly check of the hemogram and liver enzymes.

If ABZ is not available or not tolerated, MBZ, the first BMZ tested against *Echinococcus*, may be used at a dosage of 40-50 mg/kg body weight, in three divided doses during fat-rich meals. Costs of BMZ and repeated examinations may be prohibitive in countries with limited resources. Praziquantel (PZQ) 40 mg/kg once a week in combination with ABZ seems more effective in killing protoscoleces than ABZ alone[125]. Other clinical studies evaluating this combination are available but they do not clarify whether PZQ has a pharmacological effect in its own right or acts only by enhancing ABZ absorption[126]. The usefulness of PZQ to avoid secondary echinococcosis needs confirmation[127].

Watch and wait

Recent expert opinion recommends that inactive CE4-CE5 cysts that are asymptomatic and uncomplicated should be left untreated and monitored regularly by imaging techniques, using the so-called "watch-and-wait" approach[56,59]. The rationale of leaving uncomplicated, inactive cysts untreated and solely monitored over time follows the observation that up to 20% of cysts become spontaneously inactive without any treatment and such cysts are likely to remain stable over time[18,26,118,120,128-130].

Follow-up

In chronic conditions such as CE, follow-up is crucial in order to evaluate the efficacy of treatment. The follow-up should start with a short interval (every 6 mo for the first 2 years) and continue with a longer interval (once a year), but this needs to be adjusted to the patient's setting. In referral centers, follow-up includes US imaging and serology; for specific patients (*e.g.*, with abdominal gas, obesity, multiple cysts, and so on) it may also include CT or MRI.

Long-term follow-up, generally longer than 5 years, is required to evaluate local recurrences which have been reported up to 10 years after apparently successful treatment[14].

CLINICAL DECISION-MAKING IN HEPATIC CE

CE can be very difficult to treat and even more difficult to cure for a number of reasons. The disease is complex and dynamic, with an evolving phase and quietly growing cysts, followed by an involution process during which the parasite is gradually dying, leaving behind a solidified, often calcified cyst or a scar.

Each successive active cyst stage carries its own risks for serious and even life-threatening complications. This variation during the CE disease process leads to a wide range of treatment modalities with an equally wide range of technological and training backgrounds necessary for implementation and delivery. As a result of all of these issues, no "one size fits all" management approach is available, and a stage-specific approach currently appears to be the best way to manage this condition[26].

Technical and economic difficulties are encountered in countries with limited resources where the patient load is greatest: here CE is defined as a *neglected disease*. Problems in acquiring clinical competence in countries where few patients suffer from the disease are also an obstacle: in these settings CE is an *orphan disease*[26]. Further complicating matters is the fact that CE is a chronically neglected disease. Investment in research is very low compared to what is needed based on estimated burden of disease[5]. The latter is very difficult to gauge because the true incidence is unknown. Acute cases have never been recorded because they are clinically silent and only the prevalence can be assessed, although often with great difficulties due to poor access to healthcare

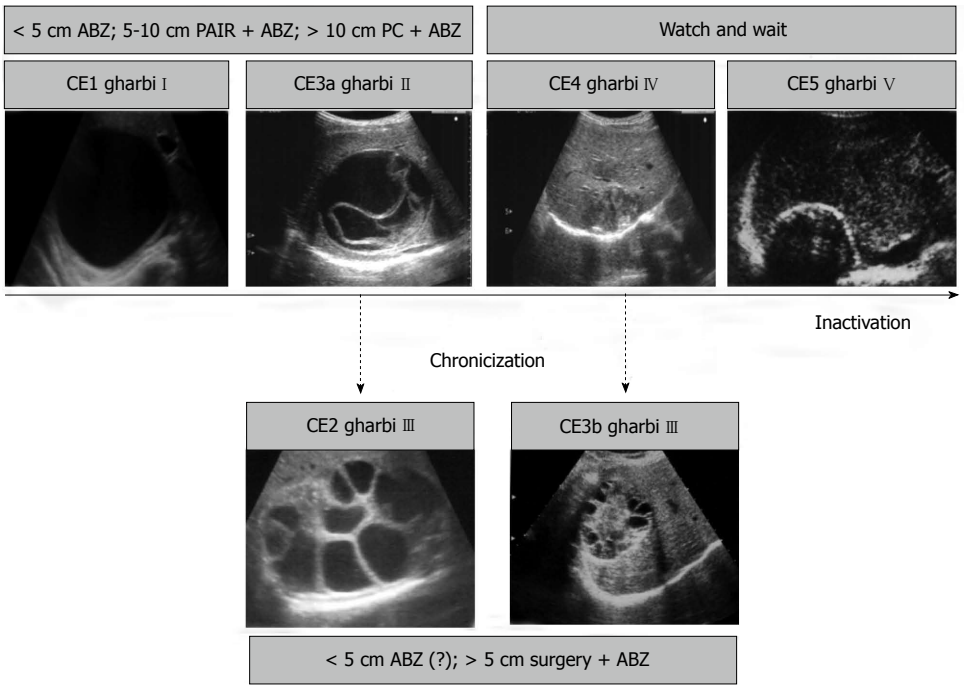

Figure 6 Schematic representation of the natural history of hepatic cystic echinococcosis and suggested treatments. Solid black arrow indicates natural evolution toward inactivation; black dashed arrows indicate evolution of therapy-unresponsive chronic stages. US images: cyst ultrasound classifications according to World Health Organization Informal Working Group on Echinococcosis[23] (in bold) and Gharbi *et al*[22]. Gray boxes: suggested stage-specific approach to uncomplicated hepatic CE[59]. ABZ: Albendazole; PAIR: Puncture, aspiration, injection of scolecidal agent, re-aspiration; PC: Permanent catheterization.

and underreporting[3]. The best solution to this problem is likely the setting up of national CE registries modeled on the European Register for Alveolar Echinococcosis. We have recently set up the Italian Register for Cystic Echinococcosis: http://www.iss.it/riec/), and preliminary results of systematic enrolment of CE patients seen in Italian hospitals will be published in the near future. However, such initiatives require resources and funding, both difficult to come by when dealing with a neglected disease[5].

OPEN ISSUES IN STAGE-SPECIFIC APPROACH

Although the evidence base for clinical decision-making is still at the level of expert opinion, clinical management of hepatic CE patients is facilitated by the standardization of US classification, enabling clinicians to identify the most rational option on the basis of cyst stage[26,131]. The stage-specific treatment approach for uncomplicated cysts of the liver can be summarized as follows (Figure 6).

Small (< 5 cm) univesicular CE1 and C3a cysts tend to respond well to ABZ treatment, while larger cysts are treated preferentially with PAIR plus ABZ. Giant cysts (> 10 cm) should be treated with a catheter left in place until the drainage is minimum, usually about 3 wk.

Surgery should be reserved for complicated cysts, including those with rupture or high risk of rupture, fistulization, compression of vital organs or vessels, hemorrhage, or bacterial infection. Surgery is also an option for cysts poorly responsive to medical or percutaneous treatment when a "watch and wait" approach is not viable because of poor access to healthcare.

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P- Reviewers: Castiella A, Chetty R, Diamantis I, Tsuchiya A
S- Editor: Gou SX **L- Editor**: Cant MR **E- Editor**: Wang CH

World Journal of Hepatology

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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4254/wjh.v6.i5.306

World J Hepatol 2014 May 27; 6(5): 306-314
ISSN 1948-5182 (online)

REVIEW

Metabolic syndrome and non-alcoholic fatty liver disease in liver surgery: The new scourges?

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Received: November 9, 2013 Revised: January 1, 2014
Accepted: January 17, 2014
Published online: May 27, 2014

Abstract

The aim of this topic highlight is to review relevant evidence regarding the influence of the metabolic syndrome (MS) and its associated liver manifestation, non-alcoholic fatty liver disease (NAFLD), on the development of liver cancer as well as their impact on the results of major liver surgery. MS and NAFLD, whose incidences are significantly increasing in Western countries, are leading to a changing profile of the patients undergoing liver surgery. A MEDLINE search was performed for relevant articles using the key words "metabolic syndrome", "liver resection", "liver transplantation", "non alcoholic fatty liver disease", "non-alcoholic steatohepatitis" and "liver cancer". On one hand, the MS favors the development of primary liver malignancies (hepatocellular carcinoma and cholangiocarcinoma) either through NAFLD liver parenchymal alterations (steatosis, steatohepatitis, fibrosis) or in the absence of significant underlying liver parenchyma changes. Also, the existence of NAFLD may have a specific impact on colorectal liver metastases recurrence. On the other hand, the postoperative period following partial liver resection and liver transplantation is at increased risk of both postoperative complications and mortality. These deleterious effects seem to be related to the existence of liver specific complications but also higher cardio-vascular sensitivity in a setting of MS/NAFLD. Finally, the long-term prognosis after curative surgery joins that of patients operated on with other types of underlying liver diseases. An increased rate of patients with MS/NAFLD referred to hepatobiliary units has to be expected. The higher operative risk observed in this subset of patients will require specific improvements in their perioperative management.

Key words: Metabolic syndrome; Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Neoplasia; Hepatocarcinoma; Liver surgery; Complications; Morbidity

Core tip: The metabolic syndrome (MS) and its hepatic manifestations, non-alcoholic fatty liver disease (NAFLD), are increasingly observed in Western countries. Both MS and NAFLD could favor the development of primary liver malignancies and may also lead to end-stage liver disease. These patients are at higher operative risk because of underestimated postoperative liver related complications but also specific increase in cardio-vascular complications. Specific improvements in the perioperative management of these patients are required in order to improve the operative results.

Cauchy F, Fuks D, Zarzavadjian Le Bian A, Belghiti J, Costi R. Metabolic syndrome and non-alcoholic fatty liver disease in liver surgery: The new scourges? *World J Hepatol* 2014; 6(5): 306-314

Available from: URL: http://www.wjgnet.com/1948-5182/full/v6/i5/306.htm DOI: http://dx.doi.org/10.4254/wjh.v6.i5.306

INTRODUCTION

The prevalence of the metabolic syndrome (MS) is reaching epidemic levels in Western Europe and Northern America, where it is reported to be as high as 25% in the general population[1]. The MS is a constellation of clinicobiological features closely related to insulin-resistance and includes dyslipidemia, hypertension, glucose intolerance and central obesity[1]. Non-alcoholic fatty liver disease (NAFLD) represents the hepatic manifestation of the MS. NAFLD pathological alterations, which range from simple steatosis to steatohepatitis, may lead to fibrosis and end stage liver disease[2]. As its incidence parallels that of the MS, NAFLD is currently becoming one of the first chronic liver diseases in Western countries and therefore has a major health impact[3]. Also, both MS and NAFLD have been suggested to be directly or indirectly associated with the development of primary liver malignancies[4-7]. For all these reasons, it is likely that more and more of these patients will be referred to hepatobiliary (HPB) and liver transplant units in upcoming years[8].

The increasing prevalence of MS/NAFLD and MS/NAFLD-related liver tumors is not the only issue related to these disorders. Despite numerous advances in the fields of hepatology, perioperative management and liver surgery, the impact of both MS and NAFLD on the postoperative course of patients undergoing liver surgery has long been neglected. As a matter of fact, it is only recently that evidence suggesting a specific and underestimated risk regarding postoperative morbidity and mortality in the setting of liver surgery has been released[8-13]. In that sense, it seems crucial that gastroenterologists and surgeons should be fully aware of the existence of MS and NAFLD as well as their negative impact on the postoperative course in order to optimize the perioperative management of concerned patients and to prevent any avoidable morbidity/mortality.

The objectives of this review are therefore: (1) to provide comprehensive insights regarding the current standards and issues in the diagnosis of both MS and NAFLD; (2) to clarify their respective impact on tumor progression as well as their influence on postoperative outcome; and (3) to discuss the measures which should be undertaken in upcoming years in order to improve the results of surgery.

DEFINITIONS AND ISSUES

Metabolic syndrome

The definition of MS has evolved during the past decade. Current consensual criteria for its diagnosis are summarized in Table 1. These include central (or android) obesity, hypertension, dyslipidemia, with either increased triglycerides level or decreased high density lipoprotein cholesterol level, and glucose intolerance[1]. Even although the presence of at least 3 out of 5 criteria of the consensual definition are required to define the MS[1], both liver histological manifestations and influence on surgical outcomes after liver surgery may occur in patients presenting with individual components of the MS. Indeed, fatty liver disease may also occur in patients with isolated diabetes mellitus (DM)[14], hypertriglyceridemia[15] and obesity[16,17]. Likewise, higher perioperative morbidity or mortality rates after liver resection are reported in patients with only DM[18,19] or overweight/obesity[20,21], whereas our groups found the association of just 2 disorders to be related to poor outcome of surgery[13,22].

Interestingly, most of the medical and surgical studies do not always gather all these consensual criteria but rather use substitutes for convenience. Such substitutes may lead to a certain degree of confusion. For example, it is frequently assumed that patients receiving statin or fenofibrate medication have dyslipidemia[8,11] and that patients receiving antihypertensive therapy have hypertension. However, some of these patients may receive such medications for primary cardiovascular prevention or renal protection. In the same way, central obesity, which reflects visceral adiposity, it is often measured using the BMI and various cut off values are proposed[8,12,13]. Yet, BMI does not allow distinguishing central obesity, which is a metabolic disorder included in the MS, from peripheral obesity. In that sense, circumferential waist appears to be more reliable and should be preferred[23,24]. Finally, the terms hyperglycemia and insulin-resistance are often used indiscriminately, whereas some authors suggest that they should not. Hence, the presence of insulin-resistance should be routinely assessed using the homeostasis model assessment of insulin resistance[25] whenever hyperglycemia is found.

NAFLD

NAFLD has emerged as one of the most frequent forms of chronic liver disease in Western countries[5,6] and should be considered in cases of fatty infiltration exceeding 5% of the liver parenchyma at histology in the absence of previous or ongoing significant alcohol consumption[26]. Although NAFLD is considered the hepatic manifestation of the MS, other conditions, including chronic hepatitis B and C infection[27,28], irinotecan based chemotherapy[29,30] and several other medications, including methotrexate, tamoxifen or amiodarone[31,32], may also lead to fatty liver disease and should be meticulously ruled out. NAFLD, which encompasses a wide spectrum of diseases ranging from simple steatosis to non-alcoholic steatohepatitis (NASH)[26], can progress to cirrhosis and may lead to end-stage liver disease[5,6]. Histological analysis remains the gold standard for the assessment of NAFLD and should be performed by a trained pathologist[33]. Several histological scores might be useful for diagnosis. The most frequently used score is the non-alcoholic liver disease activity score (NAS) proposed by Kleiner *et al*[26], which is a semiquantitative,

Table 1 Diagnostic criteria of the metabolic syndrome

Criteria	Consensual criteria definition[1]	Other non-consensual criteria
Central obesity	Abdominal waist[2] > 102 cm (United States) or 94 cm (Europe) in men > 88 cm (United States) or 80 cm (Europe) in women	Different cutoff values of BMI ⩾ 28 or ⩾ 28.8 or ⩾ 30 kg/m^2
Dyslipidemia	Triglycerides ⩾ 150 mg/dL (1.7 mmol/L) HDL cholesterol < 40 mg/dL (1.03 mmol/L) in men < 50 mg/dL (1.29 mmol/L) in women	Statin or fenofibrate medication[3]
Hypertension	Blood pressure > 135/85 mmHg	Any antihypertensive therapy[3]
Glucose intolerance	Hyperglycemia Fasting glucose ⩾ 110 mg/dL, or type Ⅱ diabetes	Any diabetes Any antidiabetic therapy (oral or insulin)

[1]Diagnosis of metabolic syndrome (MS) requires at least 3 out of 5 criteria; [2]Other cut off values have been established for Asians and Latin Americans; [3]These treatments can be taken in account for the diagnosis of MS unless if given in preemptive purpose.

histology-based score system including three parameters, namely steatosis (on a scale of 0-3), lobular inflammation and hepatocellular ballooning (on a scale of 0-2 each) and therefore ranges from 0 to 7. Likewise, Bedossa *et al*[34] recently published a histopathological algorithm and scoring system for evaluation of liver lesions in morbidly obese patients.

NASH

NASH is considered the result of long-lasting inflammation. It is characterized by several histological alterations, including steatosis, lobular inflammation and ballooning, and may also be associated with fibrosis. Even although the diagnosis of NASH was initially suggested for NAS values of 4 or 5[26], there is an ongoing debate regarding the accuracy of NAS in assessing NASH. Interestingly, Brunt *et al*[33] have emphasized that the diagnosis of NASH based on evaluation of patterns as well as individual lesions on liver biopsies did not always correlated with threshold values of the semi quantitative NAS. Moreover, NAS does not include other histological alterations often present in NAFLD, such as microcirculation modifications, which are not routinely reported by pathologists[35]. Thus, rather than being based on the NAS value alone, the differentiation between NASH and no-NASH should rather take into account the pathologist report[33].

Identification of NASH in patients with MS/NAFLD

Since the increasing incidence of both MS and NAFLD in Western populations de facto puts a great amount of patients at risk of developing NASH, any large scale screening policy aimed at obtaining histological diagnosis of NAFLD does not seem reasonable. Furthermore, the accuracy of histology in identifying NASH is suboptimal as both inter-observer variations[36] and discrepancies from one sample to the other within the same parenchyma may occur[37]. In order to increase cost/effectiveness and accuracy of diagnosis, and also to avoid the intrinsic invasiveness of biopsy, there has been significant interest in identifying non-invasive methods of predicting liver histology in patients with suspected NASH. Hence, numerous biological (alanine aminotransferase/aspartate aminotransferase ratio, FIB-4, analysis of organic compounds in breath)[38] and imaging techniques (magnetic resonance imaging (MRI) for quantification of liver steatosis[39] or magnetic resonance spectroscopy) have been proposed for the detection of underlying parenchymal changes among patients with MS, but none has become the "gold standard". In particular, although MRI has shown high accuracy in detecting steatosis, its effectiveness in evaluating (and possibly ruling out) fibrosis is questionable in the presence of fat[40].

MS/NAFLD INFLUENCE ON CARCINOGENESIS

The association between individual components of the MS, such as diabetes[41] and being overweight[42], and an increased risk of cancer has long been known. More recently, it has been suggested that the MS itself was implicated in carcinogenesis, especially in the liver[4]. Indeed, two recent series have shown that the MS itself was associated with an increased risk of developing of both HCC[3] and intrahepatic cholangiocarcinoma[43]. In particular, HCC incidence in patients with MS is reportedly 2-4 fold higher than in general population[7].

How the MS acts to promote carcinogenesis remains to be fully elucidated. Several genetic mechanisms are supposed to be involved in MS-related carcinogenesis. Firstly, direct oncological effects may play a role in the carcinogenesis by loss of tumor suppression genes, deregulation of IL-6 signal or inhibition of JNK1 phosphorylation[22]. This mechanism is supposed to be at the origin of malignant transformation of liver cell adenoma in men[44]. Secondly, the MS has been reported to be associated with low-grade, chronic systemic inflammation, implying a serum increase of inflammatory cytokines, such as TNF-α and IL-6[5], and a decrease in anti-inflammatory ones, including adipocytokines[45].

Interestingly, most studies focusing on HCC occurring in patients with MS (or arising in a context of NAFLD) have consistently reported that 30%-60% of the patients displayed no feature of severe underlying fibrosis[7,8,22,46]. More surprisingly, almost 20% of the

patients had a normal underlying liver parenchyma after conventional pathological examination. In this setting, HCCs furthermore tended to be isolated and of large size[8,22]. These findings seem to indicate that several different pathways may be implicated in liver carcinogenesis in patients with MS, as suggested by the inconstant presence of various histology alterations.

Although not always present, NASH related cirrhosis may possibly be considered a precancerous lesion as it is associated with a yearly incidence of HCC as high as 2.6%[5], leading to a cumulative 5-year incidence ranging from 7.6%[47] to 11%[48]. In the event of NASH related cirrhosis, both presence and pattern of hepatic iron deposition[49] have been incriminated to further accentuate parenchymal changes, thus promoting liver carcinogenesis.

Virus infection may also play an indirect role in tumor development in patients with MS. In particular, the specific subset of patients with chronic hepatitis C virus (HCV) infection developing an HCC is worth being mentioned. Several authors have emphasized that chronic HCV infection was associated with fatty infiltration of the liver parenchyma in 50%-70% of cases, including massive steatosis and NASH[27,28,50,51]. A non-negligible number of the latter display the so-called "viral steatosis" as a consequence of virus interference with fat metabolism (in the absence of pre-existing metabolic disorders). Thus, in this setting, steatosis itself could be responsible for the occurrence of secondary insulin-resistance and systemic inflammation. Even although the "viral steatosis" has been shown to regress after viral eradication[52], its existence has been incriminated in recurrence of HCV related HCC[53] after curative surgery. However, since steatosis and lobular inflammation may be found in HCV infection regardless of MS/NAFLD, the supposed association between HCC, HCV and NAFLD could be more a statistical artifact than a real oncogenic mechanism. Taken together, the supposed pathway from viral infection to viral steatosis and HCC, as well as the possible mechanisms finally leading to HCC development (fibrosis, inflammation or induced insulin-resistance), still remain to be assessed.

Finally, the association between MS, NAFLD and colorectal liver metastases (CLM) has to be considered. Indeed, whereas several studies on colorectal cancer patients analyzed the impact of 5FU + irinotecan based chemotherapy on the development of steatohepatitis[28,30], it is only recently that studies have focused on the specific oncological influence of both MS and NAFLD on CLM, with various results. On one hand, Hamady *et al*[54] found that liver steatosis was associated with a 1.3 fold risk of local recurrence following liver resection for CLM, regardless of the chemotherapy regimen used. On the other hand, Viganò *et al*[55], studying the impact of chemotherapy-related liver injuries, pathological tumor regression grade and micrometastases on long-term survival, found that higher grade (2-3) steatosis was significantly associated with improved 5 year overall survival compared to lesser steatosis (grade 0-1) after resection of CLM (52.5% *vs* 35.2%, $P = 0.002$). Even although these studies lacked specific histological assessment of NAFLD and precise identification of metabolic disorders, the observed results clearly reflect the growing enthusiasm of surgeons in exploring the impact of NAFLD on the long-term outcomes of patients with CLM.

MS/NAFLD IMPACT ON OUTCOME OF LIVER SURGERY

The impact of individual components of the MS and liver steatosis on the postoperative course following liver resection has been extensively investigated[18,56-60]. Accordingly, it has been established that liver surgery provided poorer results in patients affected by diabetes[18] or obesity[56,57] than in otherwise healthy patients. Similarly, several studies have highlighted that steatosis per se was a risk factor for postoperative complications after major hepatectomy[58-60]. In experimental models, liver fatty infiltration, such as mild or severe steatosis, has been found to be associated with lower regenerative ability following portal vein occlusion, elevated sensitivity to ischemia-reperfusion injury and higher hepatocellular injury after partial liver resection[61]. Nevertheless, it is only recently that surgeons have focused on the results of surgery, liver resection and transplantation in the specific subset of patients with MS or NASH.

Liver resection

Table 2 summarizes the results of recent series analyzing the early outcome of patients undergoing liver resection in a setting of MS/NASH[8-13]. Of these six series, three aimed at assessing the influence of the MS on outcome[8,12,13], whereas the remaining three aimed at evaluating the impact of histological modifications, including NAFLD and NASH[9-11]. The fact that data concerning metabolic disorders (and MS) and liver histology were gathered together in only half of the series[8,11,13] emphasizes the absence of clear understanding of the relationship between MS and MS-related liver disease. In these studies, mortality after liver resection varied from 3% up to 30% and was related to the primarily studied parameter, *i.e.,* MS, NAFLD or NASH. In this setting, it has been recently suggested that MS patients with a NAS > 2[8] or those with an histological diagnosis of NASH[11] had a 2.7-fold higher risk of experiencing liver related but also cardio-respiratory complications than those with normal underlying parenchyma. Hence, it seems that steatohepatitis rather than simple steatosis was a risk factor for postoperative complications[11]. Even if these recent findings may appear to be in opposition with previously published results maintaining a negative impact of steatosis on outcome[58-60], it is likely that the poor assessment of inflammatory changes in the underlying steatosic parenchyma may have biased older series. On the opposite hand, the progressively increasing degree of parenchymal change, damage and inflammation from steatosis to steatohepatitis is nowadays considered as a continuum, which progressively and proportionally increases overall

Table 2 Studies focusing on liver resection in a context of metabolic syndrome, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis

Ref.	Endpoint	Underlying parenchyma	Assessment of metabolic factors	Morbidity			Mortality
				Overall	Liver related	CV and respiratory	
Wakai *et al*[9]	Influence of the underlying liver on liver resection	NAFLD (n = 17)	BMI	59%	47%	6%	12%
Neal *et al*[10]	Influence of the underlying liver on right trisectionectomy	NASH (n = 9)	All factors	NA	NA	NA	22%
Reddy *et al*[11]	Influence of the underlying liver on liver resection	Simple steatosis (n = 72)	All factors	35%	19%	28%	4%
		NASH (n = 102)		57%	28%	13%	4%
Bhayani *et al*[12]	Influence of the MS on liver resection	NA	MS (n = 256)	29%	NA	22%	6%
			No MS (n = 3.717)	23%		15%	2%
Zarzavadjian Le Bian *et al*[13]	Influence of the MS on right trisectionectomy	NAFLD (n = 27)	> 2 MS factors (n = 30)	60%	53%	NA	30%
			≥ 3 MS factors (n = 13)	NA	NA	NA	54%
Cauchy *et al*[8]	Influence of the MS on liver resection	NASH (n = 16)	MS (n = 62)	58%	21%[1]	17%[1]	11%

[1]Major complications: Clavien Ⅲ-Ⅴ. MS: Metabolic syndrome; NAFLD: Non-alcoholic fatty liver disease; NASH: Non-alcoholic steatohepatitis; CV: Cardiovascular; NA: Not applicable.

postoperative morbidity/mortality.

Intuitively, not only the "quality" but also the "quantity" of liver remnant should be considered. In fact, it has been recently suggested that NASH was independently associated with both higher postoperative liver insufficiency and mortality following right hepatectomy (including extended right hepatectomy)[13], and trisectionectomy[10], although a (usually) "safe" amount of liver parenchyma was left in place. This result clearly emphasizes the worse tolerance to extended resection of fatty and inflammatory livers. This feature may be of particular importance in the case of HCC developing in a MS/NAFLD context, where large lesions often require major resections[8,22].

Considering cardiovascular morbidity/mortality, it has been shown that NASH was an independent risk-factor for the development of coronary artery disease and calcifications regardless of the degree of visceral adiposity[62,63], thus leading to a higher incidence of cardio-respiratory events following liver resection. Possibly, the recently described hemorheological alterations occurring in MS patients, including increased erythrocyte aggregation[64,65], may play a role in ischemic cardiac events.

Liver transplantation

NASH can progress to cirrhosis[2,4] and may lead to end-stage liver disease requiring liver transplantation (LT). During the last decade, the rate of LT performed for NASH related end-stage liver disease has dramatically increased from about 3% in the early 2000s up to 19% in 2011[2]. Currently, non-alcoholic steatohepatitis is the third most common cause of LT in the US and is on pace to become the most common within the next two decades in Western countries[66].

LT in NASH patients has peculiar aspects. Compared with other patients undergoing LT, recipients with NASH tend to be older[67] and obviously have a higher frequency of metabolic disorders[62]. In this setting, procedures significantly last longer and are associated with higher blood loss and longer post-transplantation hospital stay[62]. Accordingly, 30 d mortality after LT in patients with NASH tends to be higher than that for other indications[68]. Several studies have reported increased liver related morbidity rates in NASH patients, such as acute rejection rates[67], but also extra-hepatic complications, including sepsis and renal dysfunction[69]. Similarly to patients undergoing liver resectional surgery, NASH patients also have a higher likelihood of developing cardio-vascular complications after LT[62,67,69]. These events, which mainly occur within the first year after LT, have been reported to be responsible for as high as 50% of the total mortality following LT[62]. The relationship between MS/NASH and cardiovascular morbidity seems more complex than a generic multi-organ vascular disorder due to MS, as suggested by the significantly higher occurrence of cardiovascular events associated with MS whenever NASH is present[70]. In fact, similarly to what has been observed after LR, NASH is nowadays thought to put patients at an even higher risk of cardio-vascular complications, regardless of comorbidities and patient-specific cardiac risk[62]. Here again, it is likely that the degree of inflammation in the underlying liver represents a key factor in the occurrence of increased cardiovascular sensitivity.

Long-term results of LT following transplantation for NASH are encouraging. One, three and five year survivals after LT for NASH range from 84%-87.6%, 75%-82.2% and 70%-76.7%, respectively, and are at least similar to that observed for LT for other traditional indications[2,62,67,68,71]. Even more remarkable, LT for HCC developed in patients with NASH seems to provide excellent long-term outcomes with higher survivals compared with patients transplanted for HCV related HCC[72]. These observations could be the result of less aggressive tumors in NASH patients with lower micro vascular invasion and decreased rates of poorly differentiated lesions[8,72].

LT in patients with NASH related cirrhosis presents peculiar issues, including cirrhosis recurrence, to be discussed separately. Recurrent disease after LT for NASH

related cirrhosis has been reported to occur in as high as 34% of recipients[68,73]. There is little information detailing the occurrence and histological evolution of NAFLD recurrence after LT and the long-term natural history of NAFLD recurrence itself is unclear[74]. Nevertheless, in these patients, recurrence is often associated with the presence of the MS or its individual components[73]. Accordingly, recurrence should be further evaluated in larger studies, with special emphasis on management of MS and secondary prevention strategies[73].

WHICH IMPROVEMENTS SHOULD BE UNDERTAKEN IN UPCOMING YEARS?

Both MS and NAFLD/NASH adversely affect short and long-term results of liver surgery. Considering that the rate of patients presenting with such conditions will keep on increasing in upcoming years, it appears crucial that specific measures should be undertaken in order to improve those unsatisfactory results. Above all, the worse tolerance to extended resection of fatty and inflammatory livers (as a consequence of lower regenerative ability) requires that this issue should be attentively pondered in the preoperative planning of surgical strategy whenever a major resection is needed. Unfortunately, the culture of considering just MS or steatosis (even without liver biopsy confirmation) a potential risk factor for major surgery has not already entered clinical practice, even in specialized environments. Addressing this issue, our group has recently shown that MS patients operated on for HCC less frequently underwent preoperative PVE when they displayed a NAS > 2 without severe fibrosis compared to those with severe underlying fibrosis, suggesting that these latter patients would probably benefit from a better anticipation of their operative risk, especially in cases of planned major LR[8].

In general, preventative measures to reduce MS/NAFLD related morbidity/mortality should include: (1) better characterization of the underlying parenchyma using invasive or non-invasive means knowing that patients with inflammatory fatty liver even without severe fibrosis are at similar operative risk as those with severe underlying fibrosis; (2) targeted perioperative management, including complete preoperative cardio-vascular work-up and intraoperative cardio-vascular and pulmonary monitoring; and, finally (3) specific "NAFLD-tailored" perioperative surgical care, such as parenchymal sparing resections, wide use of liver volume modulation techniques, including portal vein embolization and portal vein ligation, but also targeted medical therapies developed in order to improve the tolerance of LR. Concerning this latter issue, a recent experimental study has highlighted the benefits of omega-3 acids in reducing severe steatosis in a preoperative setting leading to improved liver regeneration and functional recovery following partial hepatectomy[75]. These encouraging preliminary results still require confirmation in a clinical setting but may already be considered a promising future field of research.

Concerning the relationship between MS/NAFLD and neoplastic disease, several strategies should be developed in order to prevent both occurrence and recurrence of primary liver cancer in MS/NASH patients. Even although it is generally recommended that overweight and obese patients with NAFLD lose 7%-10% of their body weight by dietary modification and exercise over the course of 6-12 mo, the paucity of data makes it difficult to make evidence-based recommendations about dietary modification and exercise to treat NAFLD and NASH[76]. In fact, medical research has mainly focused on reducing NASH in MS patients using medical therapies. Several randomized controlled trials have shown significant downstaging of NASH following the administration of specific medications, including vitamin E and pioglitazone[77-79]. Retrospective studies have shown that the use of biguanides, such as metformin, was associated with HCC risk reduction among diabetic patients[80,81]. Experimentally, metformin has been shown to provide antineoplastic effects through deregulation of the m-TOR pathway[82,83]. Hence, in a context of MS/NAFLD related HCC, metformin would theoretically represent an ideal preventative therapy reducing both incidence of HCC following parenchymal alterations or systemic inflammation and also providing inherent antitumoral properties. Nevertheless, despite the encouraging results of all these medications and the possible future development of others that are even more effective, it should be kept in mind that none have currently been tested in a surgical context. In fact, the prolonged time interval required by medications to obtain relevant effects on liver parenchyma possibly reducing morbidity definitely questions its applicability in a surgical environment prior to (or after) surgery. This consideration gains interest if one considers that the great majority of patients undergoing major liver surgery (LR and LT) presents with cancer or end stage liver disease, needing prompt management. Obviously, any medical/preventative strategy should ideally require a large-scale evaluation in a surgical setting.

CONCLUSION

Both the pro-oncogenic effect on the underlying liver and the rising incidence of MS/NASH imply that an increased number of patients with such conditions referred to HPB units has to be expected. The higher operative risk observed in these patients can be partially explained by both underestimated liver related risk and also high perioperative cardio-vascular and respiratory susceptibility. These unsatisfactory postoperative results will require targeted perioperative management. Such actions are justified by the observed favorable long-term outcomes.

ACKNOWLEDGMENTS

The authors would like to thank Clemence Sebag for her precious help in reviewing the manuscript.

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P- Reviewers: Anty R, Bellentani S, Fierbinteanu-Braticevici C, Trovato GM **S- Editor**: Zhai HH **L- Editor**: Roemmele A **E- Editor**: Wang CH

World Journal of Hepatology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4254/wjh.v6.i5.315

World J Hepatol 2014 May 27; 6(5): 315-325
ISSN 1948-5182 (online)

REVIEW

Management of patients with hepatitis B and C before and after liver and kidney transplantation

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Received: December 3, 2013 Revised: March 10, 2014
Accepted: April 16, 2014
Published online: May 27, 2014

Abstract

New nucleos(t)ide analogues (NAs) with high genetic barrier to hepatitis B virus (HBV) resistance (such as entecavir, tenofovir) have improved the prognosis of patients with HBV decompensated cirrhosis and have prevented HBV recurrence after liver transplantation (LT). NAs are considered the most proper approach for HBV infection in patients under renal replacement therapy but their doses should be adjusted according to the patient's creatinine clearance. In addition, physicians should be aware of the potential nephrotoxicity. However, patients with chronic hepatitis C and decompensated cirrhosis can receive only one therapeutic option before LT, as well as for Hepatitis C virus (HCV) recurrence after LT, which is the combination of subcutaneous Peg-IFN and ribavirin. Generally, therapy for HCV after renal transplantation should be avoided. Although the optimal antiviral therapy for HCV infection has not been established, attention has turned to a new, oral direct acting antiviral treatment which marks a promising strategy in prognosis and in amelioration of these diseases.

Key words: Liver transplantation; Kidney transplantation; Hepatitis C; Hepatitis B; Recurrence

Core tip: While nucleos(t)ide analogs (NAs) offer a benign course in patients with hepatitis B virus before and after liver and renal transplantation, there is still scope for improvement. The administration of high genetic barrier NAs such as entecavir or tenofovir pre-transplant and the careful patient selection for hepatitis virus immunoglobulin-free regimens post-transplant contribute to improved medical care and facilitate its provision from a practical standpoint. Concordantly, attention has turned to new treatment strategies regarding hepatitis C virus recurrence after liver and renal transplantation. The addition of oral direct acting antivirals to the existing treatment marks a promising strategy for prognosis amelioration of these patients.

Pipili C, Cholongitas E. Management of patients with hepatitis B and C before and after liver and kidney transplantation. *World J Hepatol* 2014; 6(5): 315-325 Available from: URL: http://www.wjgnet.com/1948-5182/full/v6/i5/315.htm DOI: http://dx.doi.org/10.4254/wjh.v6.i5.315

INTRODUCTION

The major breakthrough in the field of transplantation for patients with hepatitis B virus (HBV) and hepatitis C virus (HCV) is the application of nucleos(t)ide analogs (NAs) and direct acting antivirals (DAAs). NAs form the mainstay in the treatment of patients with HBV in the non-transplant setting as well as before and after liver and kidney transplantation. The preliminary data regarding the DAAs application favored its use in treatment of HCV recurrence after liver transplantation (LT) and in HCV renal transplant candidates.

Table 1 Recommendations for the management of hepatitis B and C infection before and after liver or renal transplantation

	Chronic hepatitis B		Chronic hepatitis C	
	Liver transplantation	Kidney transplantation	Liver transplantation	Kidney transplantation
Pre transplant	NAs[1]		Peg IFN ± RBV ± DAAs[3] (depending on genotype and type of DAA)	PegIFN plus very low dose RBV (plus DAAs)[4]
Post transplant	Prophylaxis and treatment		No prophylaxis[2]	
	Short term HBIG plus NA	NAs[1]	Peg IFN ± RBV ± DAAs[3] (depending on genotype and type of DAA)	RBV+ sofosbuvir (?)

[1]Entecavir or tenofovir are the advisable NAs in adjusted doses regarding creatinine clearance; [2]Therapy is indicated in fulminant cholestatic hepatitis and de novo glomerulonephritis; [3]Records for boceprevir, telaprevir and sofosbuvir. Triple combination is preferable in cases of cirrhosis (METAVIR fibrosis stages 3 and 4), cholestatic hepatitis, previous virological failure and in the presence of predictors of poor response; [4]There are only cases for the use of DAAs in renal transplant candidates. HBV: Hepatitis B virus; HCV: Hepatitis C virus; NA: Nucleos(t)ide analog; HBIG: Hepatitis virus immunoglobulin; DAAs: Direct oral acting antivirals; Peg IFN: Peg interferon; RBV: Ribavirin.

In general, the induction of immunosuppressive therapy carries the risk of HBV reactivation, leading to liver graft loss and fatal complications[1,2]. NAs have dramatically improved the clinical course of patients with HBV decompensated cirrhosis, reducing the need for LT, and have further improved the prognosis of HBV transplant patients[3,4]. At present, due to high rates of resistance[3,4], lamivudine is preferable only when short term immunosuppression is scheduled. Entecavir and tenofovir are the first choice NAs because they have very high efficacy and low resistant rates[5,6]. NAs administration implies detailed renal function monitoring. Telbivudine may improve renal function but it has an unfavorable resistance profile[7].

In regards to transplantation in patients with chronic hepatitis C (CHC), improvements in the understanding of the viral cycle have led to development of the first generation DAAs (telaprevir and boceprevir) which belong to HCV NS3/4 protease inhibitors[8,9]. Their addition to the standard of treatment [pegylated interferon (Peg-IFN) and ribavirin (RBV)] has improved the response rates in a small number of liver transplant recipients and in a few cases of renal transplant candidates. When DAAs are used, calcineurin inhibitors doses should be adjusted[10] and the hemoglobin levels should be regularly monitored. The present review focuses on the current treatment of patients with HBV and HCV before and after liver and kidney transplantation.

MANAGEMENT OF PATIENTS WITH HEPATITIS B AND C BEFORE AND AFTER LT

The management of patients with hepatitis B and C listed for LT contains a three step approach. Targeted therapy should start before transplantation and continue after transplantation, becoming more intensive immediately post-transplant when the immunosuppression is higher. Therapy escalation in an early post-transplant stage is imperative mainly for avoidance of HBV recurrence, while routine prophylactic therapy for HCV recurrence is not recommended[11,12] (Table 1).

HBV positive and HCV positive liver transplant candidates

Before transplantation, treatment aims to eliminate viral load, to keep it undetectable at the time of transplantation in order to lower the risk of HBV recurrence and improve the outcome[13,14]. HBV DNA clearance pre-transplant has reduced the rate of HBV recurrence in patients with HBV infection[15]. Similarly, HCV RNA eradication pre-transplant resulted in amelioration of fibrosis and long term survival in patients with HCV infection[13,15-18]. The suppression of HCV viremia in LT candidates and the undetectable HBV DNA at the time of LT are the most important goals for each particular infection.

The current management of patients with cirrhosis and CHB before LT is based on NAs[3,15] and modification of lifestyle, comorbidities and drug interactions[19]. Generally, the institution of NAs has ameliorated the transplant prognostic scores to such a high level that many LT candidates with CHB have delisted[20-22], presenting with great clinical improvement and better survival[23-25]. NA administration as monotherapy or in combination are the current guidelines for LT candidates with HBV decompensated cirrhosis[26-28]. The high genetic barrier antivirals entecavir and tenofovir are recommended as monotherapy. Entecavir has reduced the HBV DNA in patients with decompensated cirrhosis, has improved their underlying liver function up to 70% and has presented with very low resistant rates[22,29-31]. Tenofovir has also been an effective initiation therapy, accounting for high fibrosis resolution over five years administration[32-34] with almost negligible resistance. When administered in patients with decompensated cirrhosis, it led to virological, biochemical and clinical improvement with very good tolerance[35].

Nevertheless, entecavir should not be applied in patients with proven lamivudine-resistance because there are high chances of resistance and treatment failure[30], while tenofovir should be used with caution because of potential tubular injury and osteomalacia[34]. However, recent trials have doubted tenofovir nephrotoxicity after ten years of therapy in large groups of HIV infected patients[36,37] or even the nucleotide nephrotoxicity in LT recipients[38].

Furthermore, it has been hypothesized that an antiviral combination might achieve higher virological response rates and lower resistance rates compared to monotherapy. However, emtricitabine plus tenofovir (200 mg and 300 mg daily respectively) have not been found to have superior antiviral potency compared to entecavir and tenofovir monotherapy[35]. In addition, the higher cost of antiviral combination compared to monotherapies limits its use in clinical practice. In conclusion, all patients on NA therapy should be monitored every three months for virological response and possible virological breakthrough with serum HBV-DNA testing[39,40].

Contrary to LT candidates with CHB, patients with CHC and decompensated cirrhosis have only one therapeutic option before LT. This is the combination of subcutaneous Peg-IFN and RBV, leading to reduced cirrhosis-related complications and improving histological changes[41], but in an unsatisfactory percentage of patients (5%-33% in genotype 1 and 14%-100% in genotypes 2/3)[12,42-45]. IFN-based regimens have also been related to poor tolerability and many side effects[42,44], such as anemia, infections and neuropsychiatric disorders[46], which require either erythropoietin and granulocyte colony-stimulating factors or antibiotics to sustain drug regimen optimal doses[47]. The aim is undetectable HCV RNA or SVR at LT to reduce the frequency of HCV recurrence[13].

HBV positive and HCV positive liver transplant recipients

The primary goal in this step is the prevention of HBsAg appearance in a patient with erased HBV infection (HBV recurrence) and a new HBV DNA finding in a patient with negative HBsAg (virological breakthrough)[48]. The combination of HBV immunoglobulin (HBIG) with high genetic barrier NA (entecavir or tenofovir) for the long term is the most effective prophylactic approach for HBV recurrence prevention[49,50]. However, the high cost of HBIG and the fact that the majority of patients receive a transplant with undetectable or minimal HBV DNA since they have been on NAs before LT led to the use of short term HBIG or HBIG-free regimens in the post-transplant period. In the first case, LT recipients take a combination of HBIG and NA for a short period post-transplant, continuing with NA monotherapy long term[49]. In a group of LT recipients with low risk for HBV recurrence (only 4.5% had detectable HBV DNA at the time of LT), entecavir or tenofovir monoprophylaxis after HBIG discontinuation was similarly effective, with no difference in renal adverse events[38,49].

Regarding the HBIG-free prophylactic regimens, dual NAs such as tenofovir and emtricitabine or tenofovir plus entecavir[51-54] accounted for undetectable HBV DNA after 26 mo treatment post LT, but they did not eliminate cases of recurrence[49,52]. Entecavir and tenofovir should be the first-line options for HBIG-free prophylaxis. It is advisable that entecavir not be used in patients with previous lamivudine resistance who should be preferably treated with tenofovir. Until the optimal HBIG-free prophylactic regimen is determined, the combination of HBIG (at least for a short period) and one high genetic barrier NA appears to be the most reasonable post-transplant approach[49,55].

Physicians should individualize the therapeutic regimen according to the pre-transplant type of liver disease, the patient's viremic status and the risk of reactivation[56,57]. HBV DNA clearance and HBeAg negativity at the time of LT, fulminant HBV and hepatitis D virus coinfection may allow HBIG reduction or withdrawal strategies[48]. At present, more and more patients maintain HBV DNA undetectable peritransplant so their prognosis has improved[3]. In our clinical setting, we use maintenance therapy with entecavir or tenofovir monoprophylaxis after a short course with low dose HBIG plus entecavir or tenofovir as antiviral prophylaxis against HBV recurrence after LT. Striking techniques such as covalently closed circular DNA (cccDNA) could detect occult HBV (HBV infection with negative HBsAg test) in hepatic and extrahepatic sites early. Nevertheless, Lenci *et al*[58] showed that many patients had a recurrence after cessation of any anti-viral prophylaxis despite negative cccDNA.

Regarding HCV positive liver transplant recipients, recurrence of HCV infection occurs in virtually all patients transplanted for HCV-related liver disease after LT. Additionally, three years post-transplant, decompensation developed in 70% of recipients compared with other immunocompetent groups in which the same proportion was less than 10%[59]. Post-transplant prophylaxis (preemptive) against HCV recurrence is not recommended because randomized trials have not confirmed its superiority regarding treatment when there was recurrence and it was associated with high cost and poor tolerability[11,12,60]. Interferon (IFN) use on the basis of high immunosuppression has not been effective and has been related to sepsis and rejection episodes[13,61]. Indications for antiviral therapy are fibrosing cholestatic hepatitis and significant fibrosis[61] [METAVIR score > F1[62], hepatic venous gradient > 6[63] and liver stiffness > 8.7 kPa[64]], but not fibrosis level > 3 because those patients cannot tolerate therapy[18]. Emphasis should be given to prompt diagnosis of histological evidence of HCV recurrence. Patients with female gender, steatosis of the graft, older donor age[65-67], cytomegalovirus and human herpes virus 6 infection[68] require sustained attention with protocol graft biopsies, regardless of normal liver function tests and good clinical condition. Non-invasive diagnostic methods such as elastography, serum and molecular fibrosis markers should also be used simultaneously[47].

The combination of Peg-IFN with RBV is again the standard of care for HCV recurrence after LT. Likewise, the regimen's efficacy is frustrating because after 72 wk of administration, SVR stabilization was achieved in only 30% of recipients[69-71]. The currently used DAAs, boceprevir and telaprevir, on the top of the old regimen have shown very promising results for the treatment of HCV reinfection in LT recipients with CHC[61]. Five studies[72-76] have demonstrated that the institution of the triple regimen obtained SVR in 50%-89% of LT

Table 2 Safety and efficacy of the combined regimen, interferon, ribavirin and protease inhibitors to treat hepatitis C after liver transplantation

	Boceprevir (*n*)	Telaprevir (*n*)	Complete virological response	Side effects
Coilly *et al*[72]	18	19	58% TVR 89% BOC	Anemia 92% Infections 27% Fatal events 8%
Pungpapong *et al*[73]	31	35	86% TVR 48%BOC	Anemia 95% Infections 10% Renal dysfunction 76% Fatal events 3%
Werner *et al*[74]	-	9	88.80%	Anemia 75% Rash 33% Renal dysfunction 33%
Stravitz *et al*[75]		50	62%	Anemia 82% Renal failure Fatal events 7%
Ann Brown *et al*[76]	-	46	60%	Anemia 48% Rash 35% Pruritus 22% Renal failure 22% Infections 22% Anorectal symptoms 41%
Forns *et al*[77]	Sofosbuvir 115		78%	Fatal events 16%

BOC: Boceprevir; TVR: Telaprevir.

recipients with CHC, mostly with genotype 1, when administered for 12 to 66 wk (Table 2). Serious side effects, fatal events, were recorded in two studies[73]. Although the place of DAAs in the management of LT recipients has not been totally clarified, two reported algorithms[19,61] may guide therapy. According to them, the triple regimen should be applied in cases of cirrhosis (METAVIR fibrosis stages 3 and 4), cholestatic hepatitis, previous virological failure and in the presence of predictors of poor response. Interestingly, sofosbuvir (NS5B inhibitor) combined only with RBV with or without PEG IFN demonstrated strong antiviral potency and disease improvement of CHC recurrence in LT recipients[77]. These are all very promising data but need to be tested in large multicenter prospective trials to become the standard of care.

In line with reducing severity of HCV recurrence after LT, immunosuppression is one of the major factors that accounts for accelerated HCV recurrence. For example, both steroid boluses as well as their very rapid tapering have been associated with aggressive HCV recurrence and graft loss. Interestingly, the long term maintenance immunosuppression with azathioprine, tacrolimus and prednisolone delayed the appearance of histologically proven severe fibrosis, while the sirolimus therapy led to HCV RNA elimination without antiviral treatment[78,79].

MANAGEMENT OF PATIENTS WITH HEPATITIS B AND C BEFORE AND AFTER KIDNEY TRANSPLANTATION

HBV positive and HCV positive renal transplant candidates

Antiviral therapy advances for HBV and HCV infection on renal transplantation (RT) have indicated great benefits in pre-transplantation and post-transplantation management and results[80-83]. However, antiviral therapy for HCV is hardly tolerated by RT candidates, especially if they have comorbidities and dialysis-related complications. It may not be wise for HCV positive patients with congestive heart failure, uncontrolled diabetes and with short life expectancy to receive antiviral therapy[84,85].

HBV and HCV positive candidates for RT should preferably undergo liver biopsy. The transjugular route is preferable since coagulation abnormalities are very common[86]. Fibroscan and other noninvasive techniques are supplementary. The presence of cirrhosis precludes patients from sole RT, while in patients with decompensated cirrhosis combined liver and kidney transplantation is the recommended option[87-90].

HBV positive RT candidates should initiate antiviral therapy when HBV DNA > 2000 IU/mL or HBV DNA ⩽ 2000 IU/mL two weeks before RT[39,91,92]. Therapy should be instituted as long as immunosuppressive therapy lasts whatever the HBV DNA level is[2] or for at least the first 2 years when immunosuppressive therapy is most intense[91]. HCV positive RT candidates should receive therapy when there is active viral replication (HCV RNA positive) and a biopsy proven chronic hepatitis[93]. Before transplantation, the goal is the accomplishment of HBV DNA clearance to prevent post-transplant virological relapse and liver-related complications[26,80,94]. The disappearance of viral load is a prerequisite for a HBV or HCV positive patient on hemodialysis to be enrolled in the RT list. Therapy with entecavir, tenofovir or lamivudine on adjusted doses for renal function is included in the current guidelines for prophylaxis of HBV positive RT candidates[26,80,91,94]. The NA optimal regimen has not been pro-

posed yet, so prophylaxis may start before or at the time of RT and continue thereafter[91,92]. Entecavir should be the first line option for avoidance of short term resistance and adefovir nephrotoxicity[91], while tenofovir had better be applied in case of lamivudine resistance.

Guidelines for HCV positive RT candidates recommend treatment with interferon α (α-IFN) in adjusted doses for renal function[93,95], although studies in this population[96,97] have shown the advantage of IFN and RBV to provide persistent SVR. The very severe anemia and heart failure caused by the combinative regimen avert clinicians from using it in clinical practice[97]. However, the addition of very low doses RBV (200-400 mg three times weekly) under thorough monitoring (weekly measure of hemoglobin, application of high erythropoietin doses and iron supplementation) could result in HCV RNA clearance and allow more patients to get on to the list[93]. The preliminary results for five RT candidates with CHC treated with the triple regimen of IFN, RBV and DAAs (four received telaprevir and one boceprevir)[98,99] are very promising. Telaprevir and boceprevir has not required dose adjustment to renal function so far. After 12 to 48 wk of triple therapy, viral load disappeared in 4/5 of patients, while moderate, almost expected side-effects were noted. These were dysgeusia, diarrhea and anemia, leading to the increase of the doses of erythropoietin and the modification of RBV doses.

HBV positive and HCV positive renal transplant recipients

The high doses of immunosuppressants (steroids and anti-CD3 antibody) required to avoid graft rejection post-transplant may be responsible for rapidly progressive liver disease and fibrosing cholestatic hepatitis[100,101]. Initially, HBV positive RT recipients should be under close surveillance and continue the same treatment started before RT. Entecavir is again the therapy of choice. It has been tried in naïve, lamivudine or adefovir resistant RT recipients for 33 mo[102-106], providing excellent results regarding HBV DNA reduction, without aggravation of creatinine clearance, microalbuminuria or allograft rejection. Discontinuation of applied NA is desirable in cases of fibrosing cholestatic hepatitis and resistance, which may occur as hepatic flare and rarely as hepatocellular carcinoma (HCC) and fatal liver decompensation[105,107]. Tenofovir (245 mg daily) adapted to creatinine clearance could be a safe alternative subsequent to resistance[108] on the condition that tubular injury is of great concern. If renal allograft dysfunction is in progress and the HBV positive RT recipient presents with a low viral load, the inception of telbivudine could potentially lead to renal function recovery[20,109-111].

Therapy of HCV after RT should only be considered in RT recipients with fibrosing cholestatic hepatitis or de novo glomerulonephritis[93,112]. α-IFN alone or α-IFN plus RBV post-transplantation are contraindicated because a high percent of irreversible and steroid resistant acute allograft rejection and low efficacy levels have been recorded[113,114]. In our clinical setting, HBV positive and HCV positive RT recipients are screened for liver enzymes, bilirubin and prothrombin time at each visit. Ultrasonography with triplex of splenoportal axis and/or transient elastography is monitored annually. HBV DNA and HCV RNA as well as a-fetoprotein are tested every year. In patients with cirrhosis, endoscopy for detection or monitoring of varices is performed every 1-2 years. All HBV positive and HCV positive RT recipients should avoid alcohol and hepatotoxic drugs. In the case of fever, effective antibiotics are started immediately. Liver biopsy and modulation of antivirals is considered in patients with abnormal liver function and/or increased viral load.

SELECTION OF PATIENTS WHO NEED CLOSE MONITORING

High HBV viral load pre and peritransplant predispose to closer patient surveillance and stronger prophylactic antiviral regimens. This group of patients is more likely to progress to decompensation and to HCC[115]. It is preferable that they be treated with entecavir or tenofovir and often be monitored for signs of decompensation. In a case of severe decompensation, patients receiving antivirals are at higher risk of lactic acidosis so physicians should be vigilant. LT candidates with HCV compensated cirrhosis are more vulnerable to IFN-related hematological toxicities since the splenomegaly caused by portal hypertension magnifies the risk for cytopenias[116]. Therefore, IFN dose modification and close regular monitoring is recommended. Furthermore, therapy in patients with Child-Turcotte-Pugh (CTP) score C (or MELD score > 18) is challenging and should be carried out in dedicated and experienced centers because IFN may cause sepsis and is associated with a low sustained virological response (SVR) rate[61]. Careful monitoring should also be applied to patients with CTP score B. They need individualization of treatment decisions regarding non-genotype 1, high viral load, treatment naïve or relapse from previous antiviral therapies[13].

RT recipients with severe liver disease should receive non aggressive immunosuppressive protocols (cannot always be applied in immunologically high risk patients) and a selected immunosuppressive regimen with minimal or preferably no steroid use. All antivirals should be modified continuously regarding current renal function. Additionally, HBsAg-positive RT recipients with cirrhosis are at risk for hepatic decompensation after isolated RT and therefore they require simultaneous liver and kidney transplantation[86]. In conclusion, we should be on the alert for all HCV positive RT recipients which means screening them regularly for HCC[117], emergence of diabetes, renal thrombotic microangiopathy[118], glomerulonephritis[119,120], renal graft nephropathy[118] and sepsis[121].

SPECIAL TREATMENT CONSIDERATIONS

Generally, entecavir and tenofovir are the preferable an-

Table 3 Prophylactic schemes against hepatitis B virus recurrence after liver and renal transplantation when grafts are from hepatitis B virus positive donors

	Donor	Recipient	Prophylaxis
Liver transplantation	Anti-HBc positive	HBsAg positive	HBIG plus NA
		HBsAg negative Anti-HBc positive Anti-HBs positive	No prophylaxis
		Anti-HBc negative Anti-HBs negative	Long term lamivudine
	HBsAg positive	Anti-HBc positive	HBIG plus NA
Kidney transplantation	Anti-HBc positive	HBsAg negative	No prophylaxis Treatment when HBV DNA increases
	HBsAg positive (HBV DNA negative)	HBsAg positive	HBIG plus lamivudine
		HBsAg negative (HBV DNA) negative	Long term lamivudine

HBV: Hepatitis B virus; NA: Nucleos(t)ide analog; HBIG: Hepatitis virus immunoglobulin.

tiviral treatment for post LT or RT recipients due to its high resistance barrier, the favorable safety profile and the regression of fibrosis with long term application[34,122]. However, entecavir is not advisable for patients with lamivudine resistance and it should be applied carefully in patients with decompensated cirrhosis with MELD score $\geqslant$ 22 because cases of lactic acidosis have been recorded with its administration[115]. Tenofovir is the only effective choice practically for patients with resistance to lamivudine or any nucleoside analogue[39] but there are concerns about creatinine clearance decline and acute tubular nephropathy during long term therapy, especially in group of patients with high risk for renal dysfunction over time such as RT and LT recipients[122]. Telbivudine is the only NA with a renal protective effect but its use in the RT and LT setting has still not been tested. Other NA limitations are the indefinite course and the relatively high cost of therapy which complicate patient compliance. Similar concerns exist about the cost and efficacy of HBIG continuation in HBV positive LT recipients. The duration of HBIG prophylaxis in HBV positive LT recipients is controversial and challenging and should be discussed on a case-by-case basis. The access to optimal therapy for HCV positive RT and LT recipients is limited by the low tolerance or contraindication of IFN-based regimens and the lack of experience of the efficacy and safety of first generation DAAs. Newer DAAs (such as sofosbuvir) need further evaluation in this setting.

HBV AND HCV POSITIVE DONORS

Many studies have shown that liver grafts from anti-HBc positive donors can be used safely in: (1) HBsAg negative but anti-HBc/antiHBs positive recipients without antiviral prophylaxis[123]; (2) in HBsAg positive recipients on the condition that dual therapy HBIG and NAs is applied[123]; and (3) anti-HBc and/or antiHBs negative recipients when receiving long term prophylaxis with lamivudine, dual therapy or no prophylaxis[123,124]. Heterogeneity of data exists regarding the use of liver grafts from HBsAg positive donors[125-128].

Similarly, renal grafts from anti-HBc positive donors can be used in HBsAg negative recipients without prophylaxis[129]. It is acceptable practice for renal grafts from HBsAg positive donors to be used in HBsAg positive or HBsAg negative recipients with subsequent long term NA administration with or without HBIG[130,131]. In all cases, serial HBV DNA measurements regardless of normal liver biochemistry are required. In particular, in LT or RT recipients who are not on any antiviral prophylaxis, an increase in viral load indicates NA initiation. On the other hand, when immunosuppression is reduced and complete viral clearance has been achieved, NA interruption could be considered[103] (Table 3).

LT candidates with HCV-related cirrhosis can undergo LT from HCV positive donors if they are not HCV RNA positive because early hepatitis C recurrence may occur[132,133]. Renal grafts from HCV positive donors are acceptable only for HCV positive RT candidates[93]. In this setting, the survival of HCV positive RT recipients increases compared to their survival rates if they remain on hemodialysis[134,135]. Renal grafts from HCV positive donors should not be distributed to HCV negative recipients because many fatal liver complications have been recorded[136,137].

CONCLUSION

Current knowledge on the management of patients with HBV offers effective and safe options for liver or renal transplantation. Individualization and determination of less nephrotoxic and finite duration antiviral treatment will enhance the quality of their treatment and prognosis. Various types of vaccinations (S and pre-S antigen vaccines, DNA vaccination, T cell vaccines) and some monoclonal antibodies (exbivirumab and libivirumab) are promising for preventing HBV recurrence and are being evaluated in clinical trials. Subcutaneous HBIG and hyperimmune anti-HBs plasma may prove to be alternative options with a lower cost and the same efficacy levels. The optimal antiviral therapy has not been established yet for LT or RT candidates with CHC. The DAAs in-

stitution marks a bright new era for treatment approach of these patients. Control randomized studies involving DAAs use in patients with decompensated cirrhosis and in RT candidates and recipients are in high need. Moreover, the optimal use and benefits of granulocyte growth factors and erythropoietin in improving SVR rates should be further researched and become established practice.

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P- Reviewers: Hilmi IA, Schemmer P, Saeed T
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DOI: 10.4254/wjh.v6.i5.326

World J Hepatol 2014 May 27; 6(5): 326-339
ISSN 1948-5182 (online)

MINIREVIEWS

NS3 protease inhibitors for treatment of chronic hepatitis C: Efficacy and safety

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Received: November 2, 2013 Revised: February 8, 2014
Accepted: April 11, 2014
Published online: May 27, 2014

Abstract

A new treatment paradigm for hepatitis C is that the treatment must include an existing direct-acting antiviral agent, namely, a protease inhibitor (PI) combined with PEGylated interferon-α and ribavirin. The currently marketed PIs and PIs in clinical trials have different mechanisms of action. The development of new PIs aims for an improved safety profile and higher effectiveness. This article reviews NS3/4A protease inhibitors, focusing on major criteria such as their effectiveness and safety. Specific attention is paid to dosing regimens and adverse event profiles of PIs administered in clinical settings.

Key words: Protease inhibitor; PEGylated interferon-α; Ribavirin; Antiviral treatment; Adverse event; Response-guided therapy; Hepatitis C virus

Core tip: This article reviews NS3/4A protease inhibitors, focusing on major criteria such as effectiveness and safety. Specific attention is paid to dosing regimens and adverse event profiles of protease inhibitor administered in clinical settings.

Bakulin I, Pasechnikov V, Varlamicheva A, Sannikova I. NS3 protease inhibitors for treatment of chronic hepatitis C: Efficacy and safety. *World J Hepatol* 2014; 6(5): 326-339 Available from: URL: http://www.wjgnet.com/1948-5182/full/v6/i5/326.htm DOI: http://dx.doi.org/10.4254/wjh.v6.i5.326

INTRODUCTION

Since 2011, increased attention has been given to "direct" antiviral agents for chronic hepatitis C (HCV). Combined treatment with PEGylated interferon-α (PEG-IFNα) and ribavirin cannot be considered a standard treatment for type 1 HCV anymore. A new treatment paradigm is that the treatment must include an existing direct-acting antiviral agent (DAA), namely, protease inhibitor (PI) combined with PEG-IFNα and ribavirin.

The currently marketed PIs and PIs in clinical trials (CTs) have different mechanisms of action. The development of new PIs aims for an improved safety profile and higher effectiveness[1]. An ideal combination is an interferon-free therapy with oral once-daily agents that are highly effective and well tolerated, do not interact with the majority of well-known therapeutics, and can be used to treat concomitant disorders. The recent evolution of DAA has included a considerable improvement in their effectiveness since 2011, and in most cases, antiviral treatment (AVT) duration has decreased.

This article reviews NS3/4A protease inhibitors, focusing on major criteria such as effectiveness and safety. Specific attention is paid to the dosing regimens and adverse event (AE) profiles with PIs administered in clinical settings.

Table 1 Direct-acting antivirals approved or at the computed tomography stage (phase Ⅱ or Ⅲ)

NS3/4A protease inhibitors	Polymerase inhibitors		Inhibitors	
	Nucleotides/nucleosides	Non-nucleoside	NS5A	Cyclophilin
Generation Ⅰ:	PSI-7977 (Pharmasset)[1]	Filibuvir (Pfizer)[1]	Daclatasvir (Bristol-Myers	Alisporivir (Novartis)[1]
Boceprevir (Merck)[1]	PSI-938 (Pharmasset)[1]	VX-222 (Vertex)[1]	Squibb)	SCY-635 (Scynexis)[1]
Telaprevir (Vertex)[1]	Mericitabine (Roche/	Tegobuvir (Gilead)[1]	GS-5885 (Gilead)[1]	
	Genentech)[1]	ANA-598 (Anadys)[1]		
	IDX-184 (Idenix)	ABT-072 (Abbott)[1]		
		ABT-333 (Abbott)[1]		
Generation Ⅱ:				
Simeprevir (Tibotec)				
BI 201335 (Boehringer Ingelheim)				
Danoprevir (Roche/Genentech), studied with Ritonavir;				
Vaniprevir (Merck)[2]				
BMS-650032 (Bristol-Myers Squibb)[2]				
GS-9451 (Gilead)[1]				
GS-9256 (Gilead)[2]				
ACH-1625 (Achillion)[1]				
ABT-450 (Abbott)				
MK-5172 (Merck)[1]				

[1]Approved by the United States Food and Drug Administration; phase Ⅱ CT; phase Ⅲ CT; [2]Not studied. From Short Guide to Hepatitis C 2013, Mauss S, Berg T, Rockstroh J, Sarrazin C, Wedemeyer H.

Table 2 General protease inhibitor description with computed tomography results since 2011

PI	Genotype	PI treatment duration (wk)	Treatment duration (wk)	Treatment regimen	PEG-IFNα	Publication date
Telaprevir	1a/1b/1c/unknown	12/8	20/24/44/48	750 mg TID	(+)	2011
Boceprevir	1a/1b/unknown	24/32/44	28/36/48	800 mg TID	(+)	2011
Daclatasvir	1a/1b	24	24	60 mg/d	(+/-)	2012
Asunaprevir	1a/1b	24	24	600 mg BID	(+/-)	2012
ABT-450	1a/1b	12	12	250/150 mg/d	(-)	2013

PI: Protease inhibitor; PEG-IFNα: PEGylated interferon-α.

GENERAL STATEMENTS

Since 2011, we have seen an increase in the value placed on "direct" antiviral agents for HCV. Most of these agents are at various CT stages, with some already being integrated in routine clinical practice as a treatment standard for type 1 HCV patients (Table 1). In 2011, FDA and EMA approved the first DAA-telaprevir and boceprevir - for HCV treatment in patients infected with type 1 HCV. Randomized CTs have shown that triple therapy is not only significantly more effective for type 1 HCV patients but that it is also the only alternative for patients with previous AVT failure. One should note that in Russia, telaprevir was approved in December 2012 and boceprevir in May 2013.

NS3/4A serine protease inhibitors are divided into two classes. The first generation includes the well-studied telaprevir and boceprevir. By the time their phase Ⅲ CT was completed, these agents were already acknowledged as new AVT standards for type 1 HCV patients.

NS3/4A protease has a crucial role in the replication cycle of hepatitis C virus. It cleaves polyprotein in four sequential active sites, forming the N-terminal proteins NS4A, NS4B, NS5A and NS5B. Regarding its chemical properties, this enzyme is related to the serine protease group. For instance, it can cleave and inactivate the host proteins Trif and Cardif. Both of these proteins are important in the responses to interferon (IFN) mediated by the receptors TLR3 and RIG-I, respectively[2,3]. Additionally, NS3 is not only a protease but also a component of the replication complex for viral RNA, acting as an RNA-helicase and nucleotide triphosphatase (NTPase). Due to its impressive set of functions, NS3 protease is an attractive target for HCV therapy. The HCV RNA replication cycle and targets for direct-acting antivirals have been thoroughly described in publications by Moradpour and Pawlotsky[4,5]. Clinical trials have studied several promising molecules that inhibit HCV protease.

Table 2 reviews published CT results for ultra-novel NS3/4a PIs, including their efficacy and safety parameters[6].

FIRST-GENERATION NS3/4A PROTEASE INHIBITORS

Telaprevir efficacy

Telaprevir efficacy was studied in phase Ⅱ and Ⅲ CTs (Table 3)[6-8].

Table 3 Telaprevir: clinical parameters

RCT	Dose frequency	Duration	SVR	Possible AE
Prove 1	Each 8 h, 6 t/d	24 wk: 12 wk of triple therapy, 12 wk of conventional treatment	61%	Rash, anemia, nausea, diarrhea
Advance	Every 8 h, 6 t/d	24-48 wk: 8-12 wk of viral response-based treatment followed by conventional treatment	69%-75%	Rash, anemia, nausea, diarrhea
Illuminate	Every 8 h, 6 t/d	24-48 wk: 12 wks of viral response-based treatment: 12 wk of triple therapy followed by conventional treatment	64%-92%	Rash, anemia, nausea, diarrhea
Optimize	Every 12 h, 6 t/d	24-48 wk: 12 wk of viral response-based treatment: 12 wk of triple therapy followed by conventional treatment for 12 to 36 wk	58%-81% (depending on fibrosis stage)	Rash, anemia, nausea

AE: Adverse event.

Table 4 Adverse events under telaprevir-based therapy

Agent RCT	Telaprevir				
	Advance		Realize		Illuminate
	PR	T8/12PR	PR48	(lead-in) T12PR48	T12PR24/48
Serious AE	7%	9%	5%	12%	9%
Discontinued AVT due to AE	7%	10%	3%	15%-11%	18%
Anorectal symptoms	4%	8%-13%	7%	15%-12%	-
Taste disturbances	-	-	6%	12%	-
Anemia	19%	39%-37%	15%	30%-36%	39%
Severe neutropenia	19%	17%-14%	11%	14%-13%	-
Rash	24%	35%-37%	19%	37%-36%	37%
Fatigue	57%	58%-57%	40%	55%-50%	68%
Pruritus	36%	45%-50%	27%	52%-50%	51%
Nausea	31%	40%-43%	23%	35%-33%	47%
Diarrhea	22%	32%-28%	14%	25%-26%	30%

AE: Adverse event.; AVT: Antiviral treatment.

Treatment mode

For telaprevir-based AVT, the following regimens are used: Treatment-naive patients and relapsers: Telaprevir is started from treatment day 1 and is always combined with conventional treatment of PEG-IFN/RBV for 12 wk. If no viremia is present (HCV RNA-negative) at 4 and 12 wk, treatment duration is 24 wk. If viral load is detected (HCV RNA-positive) at 4 or 12 wk, treatment duration is 48 wk. Null responders or partial responders as well as liver cirrhosis patients: The only option for triple therapy is telaprevir for 12 wk, with a total AVT duration of 48 wk. Telaprevir-based regimens have clear algorithms for AVT early discontinuation[9]. Triple therapy must be totally canceled in the following cases: HCV RNA above 1000 IU/mL at 4 and 12 wk on triple therapy; HCV RNA-positive at treatment week 24; Viral breakthrough and/or viral load increase.

The above rules are unambiguous and must be strictly followed because they are evidence-based results that were developed after multicenter randomized CTs. If HCV RNA is present in the titers above, it indicates that the AVT is ineffective when continued treatment has no clinical or cost-effective rationale. Moreover, ongoing treatment might result in resistant strain development, as indicated by phase Ⅱ and Ⅲ CTs showing relapses and no viral response.

Safety

The AE control algorithm is important for telaprevir-based treatment. The safety profile of triple therapy has a higher AE number *vs* conventional treatment, which in the future, may be a limiting factor for first-generation PI use (Table 4).

Triple-therapy AEs have been reviewed in CT results and other recent publications[10]. Therefore, it seems necessary to dwell on some of them because developing AEs might require changes in patient management (PI or AVT discontinuation) or may be difficult to control in clinical settings.

Telaprevir has the following common AEs: rash, anemia and anorectal signs (as shown by the ADVANCED and REALIZE trials).

Telaprevir-based triple therapy increases the anemia rate by 15% to 21% *vs* control. The severe anemia rate is comparable among study arms and results in discontinued treatment in 2%-4% of cases (Table 5).

Anemia development in the compared arms is not a negative prognostic criterion for SVR. Currently, the main method for anemia control is ribavirin dose adjustment. Some experts consider that an Hb below 7.5 g/dL implies complete triple therapy discontinuation. However, the CUPIC study showed that AVT can be continued if erythropoietin and blood transfusions are used[11,12].

Rash is considered a specific AE for telaprevir-based therapy and results in 5%-7% of treatment discontinuation cases. In 50% of cases, rash appears within the first 4 wk of treatment, but rash can develop during the whole course of treatment. In some rare cases, skin signs can be classified as serious AEs.

The rash treatment algorithm depends on its severity (evaluated on the body surface involved). Mild to moderate rash is an indication for antihistamine agents, local steroid ointments and avoiding sunlight. It does not require stopping triple therapy. For severe rash, it is recommended to stop telaprevir, and conventional treatment can be continued with the provision of effective treatment with steroids (locally) and antihistamines. In case of progression and severe skin signs, treatment must be canceled.

Table 5 Boceprevir: clinical parameters

RCT	Dose frequency	Duration	SVR	Possible AE
SPRINT 1	12 pills for 3 intakes	28-wk triple therapy *vs* 4-wk lead-in phase 48-wk triple therapy *vs* 4-wk lead-in phase	54%-56% 67%-75%	Metal taste, anemia
SPRINT 2	12 pills for 3 intakes	28-48 wk: "viral response-based treatment"; "lead-in period"; if HCV RNA (-) by week 8 and 24, to stop at week 28; if HCV RNA (+), 20 wk of double therapy	67% And 44% were given abridged AVT	Taste disturbances, anemia, neutropenia

AE: Adverse event; AVT: Antiviral treatment; HCV: Hepatitis C virus.

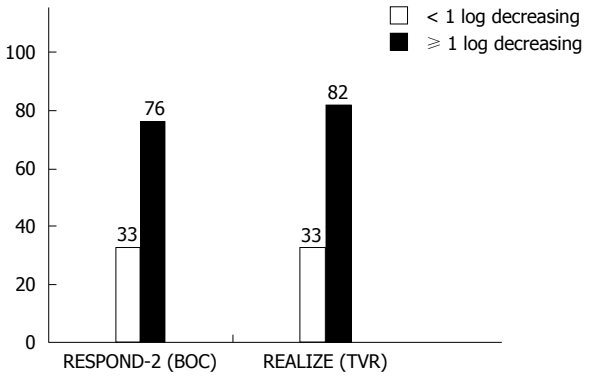

Figure 1 Hepatitis C virus RNA drop after lead-in phase (treatment week 4).

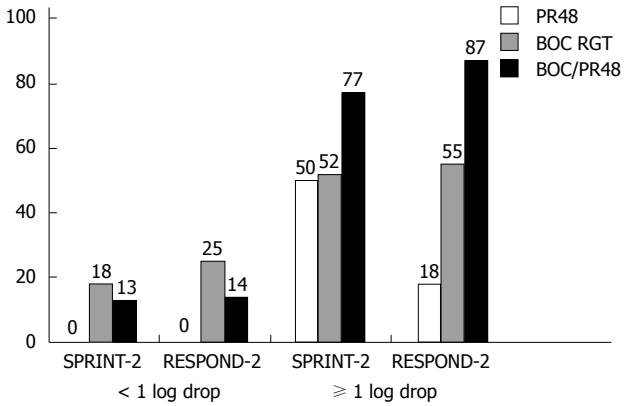

Figure 2 SVR rate after the lead-in period in patients with F3/4 fibrosis. PR: Conventional therapy (PEGylated interferon-α and ribavirin). BOC RGT: Boceprevir-based, viral response-dependent triple therapy; BOC/PR48: Boceprevir-based triple therapy for 48 wk; the results are from the SPRINT-2 and RESPOND-2 studies.

BOCEPREVIR

Efficacy

Boceprevir's efficacy was studied in phase Ⅱ/Ⅲ CTs (Table 5)[1,6]. Considering a new term, *i.e.*, the lead-in period or lead-in phase, several issues should be discussed. Triple therapy development has provided data on new sensitive response predictors. Assessing the viral load decrease after a 4-wk lead-in can allow for an accurate assessment of a patient's chances to reach SVR (Figure 1): A lead-in period enables researchers to assess conventional treatment tolerance and prognosis if PEG-IFN/RBV is safe to use. RCT results (RESPOND-2 and PROVE-2) show that a lead-in period lowers the viral load before the onset of triple therapy and delineates a patient group that should receive a shorter AVT duration. These diminish the probability of mutant, PI-resistant HCV strain development. If the viral load drops by more than 2 $\log_{10}$, this indicates high patient sensitivity to IFNα and ribavirin, which is a rationale to continue AVT as a standard treatment. However, it seems that the main objective of the lead-in period is to discern the patient groups in which conventional AVT appears to be less effective in a prognostic sense, and triple therapy makes it possible to avoid unjustified treatment costs and a non-mandatory pharmaceutical load when double therapy is continued (Figure 2).

Treatment mode

An important issue is strict compliance with discontinuation rules for triple therapy. For instance, ineffective boceprevir-based triple AVT should stopped in time to prevent the development of boceprevir-resistant HCV strains. The entire triple therapy should be canceled in the following cases (algorithm for early treatment discontinuation): (1) if the HCV RNA is above IU/mL at week 12 of AVT (triple therapy week 8); (2) if there is no aviremia at week 24 of AVT (triple therapy week 20); and (3) in case of viral breakthrough and/or viral load increase by 1 $\log_{10}$.

Safety

The SPRINT-2 and RESPOND-2 data show that boceprevir use increases the rate of taste disturbances, anemia and neutropenia[6,13] (Table 6).

Second-generation NS3/4A protease inhibitors

The development of second-generation NS3/4A protease inhibitors resulted in some hopes of improving treatment outcomes in type 1 HCV patients. This group of agents has some advantages compared to the 1st-generation NS3/4A protease inhibitors (telaprevir and boceprevir): first, the dosing mode (once a day) and second, a better tolerance profile (fewer adverse events). However, the fact that both groups of agents have both a common viral genotype as their target and similar resistance profiles restrain us from considering 2nd-generation NS3/4A protease inhibitors to be a new class of HCV protease inhibitors. Nevertheless, modern publications still use this term for a range of new therapeutic agents with improved pharmacokinetics. It is possible that after

Table 6 Adverse events under triple therapy

Agent	Boceprevir			
RCT	SPRINT-2		RESPOND-2	
	PR48	PR4/ PRB24/44	PR48	PR4/ PRB32/44
Serious AE	9%	11%-12%	5%	10%-14%
Discontinued AVT due to AE	16%	12%-16%	2%	8%-12%
Anorectal symptoms	-	-	-	-
Taste disturbances	18%	37%-43%	11%	43%-45%
Anemia	29%	49%	20%	43%-46%
Severe neutropenia	14%	24%-25%	9%	19%-20%
Rash	23%	25%-24%	5%	17%-14%
Fatigue	60%	53%-57%	50%	53.7%-57.1%
Pruritus	27%	24%-26%	17.50%	18.5%-19.3%
Nausea	42%	48%-43%	37.50%	43.8%-39.1%
Diarrhea	22%	22%-27%	15%	22.8%-23%

AE: Adverse event; AVT: Antiviral treatment.

some CTs are completed, 2nd-generation NS3/4A protease inhibitors will replace the 1st-generation agents when combined with PEG-IFN/RBV, thereby becoming the 1st generation of DAA in regimens of so-called interferon-free HCV treatment.

Simeprevir

Simeprevir (TMC435; Tibotec, Beerse, Belgium; Medivir Pharmaceuticals, Stockholm, Sweden; Janssen, Beerse, Belgium) is one of the 2nd-generation NS3/4A protease inhibitors. Simeprevir has passed phase I to Ⅲ trials in patients with 1a and 1b HCV genotypes.

Efficacy

Phase I and Ⅱ trials demonstrated potential antiviral activity for TMC435, as well as its efficacy and tolerability. TMC435's pharmacokinetic properties enable its use in once-a-day dosing[14].

To study TMC435's efficacy and safety, a phase Ⅱb trial, PILLAR [Protease Inhibitor TMC435 trial assessing the optimaL dose and duration as once daiLy Antiviral Regimen] (TMC435-C205; NCT00882908), was organized. Conducted in 13 countries in Europe, North America and Australia, it enrolled 368 naive patients with genotype 1 treated with simeprevir combined with PEG-IFN/RBV for 24 or 48 wk. Two doses of simeprevir (75 mg *vs* 150 mg) and treatment durations (12 wk *vs* 24 wk) were compared. The final analysis of the PILLAR study showed that TMC435 given in combination with PEG-IFN/RBV to naive patients with genotype 1 HCV resulted in a SVR rate that significantly exceeded that observed in patients treated with the placebo + PEG-IFN/RBV combination (Figure 3).

In 2 patient arms treated with TMC435 at 75 mg/d, the patient percentage reaching SVR in varied from 75% (12 wk) to 82% (24 wk); with TMC435 at 150 mg/d, this percentage varied from 81% (12 wk) to 86% (24 wk). In the comparison arm, the percentage of placebo-treated patients reaching SVR in 24 wk or less amounted to 65%[15].

A new publication[16] analyzing the PILLAR study

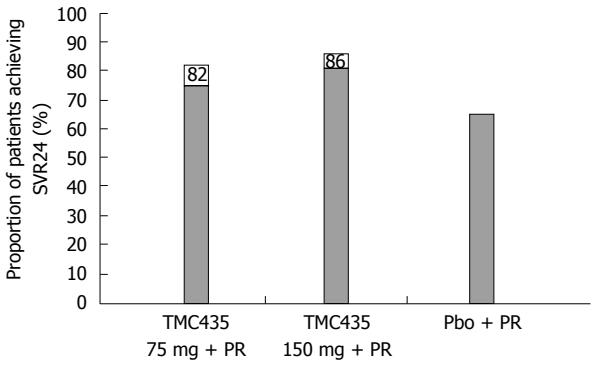

Figure 3 Portion of patients treated either with TMC435 at 75 mg/d or 150 mg/d or with placebo, combined with PEGylated interferon/ribavirin, who reached SVR24 (%) in the PILLAR study[15].

results indicated that SVR determined in 24 wk after planned treatment completion (SVR24) varied in the range of 74.7%-86.1% for all simeprevir arms *vs* 64.9% in the control. All arms treated with simeprevir for 12 or 24 wk showed a significant difference in SVR24 parameters, excluding the arm given 75 mg/d for 24 wk. Rapid virologic response (HCV RNA < 25 IU/mL, undetermined level at treatment week 4) was reached in the SMV-treated arms in 68.0%-75.6% of cases, compared to 5.2% in the placebo-treated controls. The criteria for a shortened treatment course (RGT criteria) were met in 79.2%-86.1% of the SMV-treated patients completing treatment in 24 wk. SVR24 was reached in 85.2%-95.6% of patients in these groups[16].

An international, randomized, double-blinded, controlled phase Ⅱb study, ASPIRE (TMC435-C206; NCT00980330), aimed to evaluate the efficacy, tolerability, safety and pharmacokinetics of TMC435 given in combination with PEG-IFN/RBV[17]. ASPIRE enrolled 462 treatment-experienced genotype 1 HCV patients. This arm included partial responders, prior relapsers, and patients with significant fibrosis or cirrhosis (Metavir, F4 stage). Patients were randomized to receive 100 or 150 mg of simeprevir OD or placebo for 12, 24 or 48 wk. The study arms with simeprevir treatment for 12 or 24 wk later continued treatment with PEG-IFN/RBV (control) only up to 48 wk. The SVR rate was significantly higher in all simeprevir-treated arms compared to those treated with PEG-IFN/RBV only. The best results were reached in patients treated with simeprevir 150 mg/d. For instance, SVR in prior relapsers reached 85% *vs* 37% in the control, 75% and 19% in the two subgroups of partial responders, and 51% and 19% in the two subgroups of non-responders[18]. It is important to note that a high SVR24 (31%) was found with simeprevir-based therapy in subgroups of liver cirrhosis patients and those with a previous null response, *i.e.,* those who traditionally are considered difficult to treat.

Viral breakthrough (in 42 of 43 patients) or infection relapse (in 34 of 36 patients) was associated with viral resistance development. Viral breakthrough has been noted in most studies when using protease inhibitors in

combination with conventional treatment[18]. Genotype 1a patients more often have mutation R155 as the only mutation or with other mutations, while genotype 1b patients have mutation D168V[18].

At the moment, 3 Phase Ⅲ clinical studies to study simeprevir's efficacy are known: (1) in treatment-naive HCV patients: QUEST-1 and QUEST-2; (2) in relapsers after previous PEG-IFN/RBV treatment: PROMISE; and (3) in null-responders: ATTAIN.

QUEST-1 enrolled 394 genotype 1 HCV patients with F0-F4 fibrosis (METAVIR scale) stratified by HCV subtype and genotype *IL28B*[19]. Patients were randomized to a simeprevir dose of 150 mg/d or placebo combined with PEG-IFN/RBV for 12 wk followed by PEG-IFN/RBV monotherapy. A treatment duration of 24 or 48 wk in the simeprevir arm and the placebo arm depended on treatment response at wk 4 and 12. If virus was undetected in the blood (HCV RNA < 25 IU/mL) at weeks 4 and 12, the patient met the short treatment criteria (RGT-criteria), and the treatment was finished at week 24. Treatment for 48 wk was recommended for patients who were treated with placebo instead of simeprevir. The majority of simeprevir-treated patients were compliant with the RGT criteria (85%) and completed treatment at week 24. The rapid response rate (RVR) reached 80% in the patients treated with simeprevir in combination with PEG-IFN/RBV and 12% in the patients treated with placebo and PEG-IFN/RBV. Simeprevir combined with PEG-IFN/RBV resulted in HCV elimination in more patients compared to the combination of placebo and PEG-IFN/RBV (80% *vs* 50%, $P < 0.001$). The relapse rate in the simeprevir/PEG-IFN/RBV arm was less than that in the placebo/PEG-IFN/RBV arm (9% *vs* 21%), as was the percentage of treatment failures (9% *vs* 34%). The QUEST-1 study showed that simeprevir 150 mg/d OD given along with PEG-IFN/RBV provided a high SVR12 rate, making it possible to decrease the treatment duration to 24 wk in a majority of patients (85%).

QUEST-2, a randomized, double-blinded, placebo-controlled study (NCT01290679), enrolled approximately 400 treatment-naive patients with genotype 1 HCV[20]. Patients were stratified according to genotype 1 subtype and host genotype (*IL28B*). They were given simeprevir (150 mg OD) combined with PEG-IFN/RBV (both of PEG-IFN type) or placebo combined with PEG-IFN for 12 wk followed by a PEG-IFN/RBV regimen. A treatment duration of 24 or 48 wk in both patient arms depended on the treatment response at weeks 4 and 12. If virus was undetected in the blood (HCV RNA < 25 IU/mL) at weeks 4 and 12, the patient met the short treatment criteria (RGT-criteria) and the treatment was finished at week 24. Treatment for 48 wk was recommended for patients who were treated with placebo instead of simeprevir. A majority of simeprevir-treated patients complied with the RGT criteria (91%) and completed treatment at 24 wk. The rapid virologic rate (RVR) was 79% in simeprevir/PEG-IFN/RBV patients and 13% in patients treated with placebo/PEG-IFN/RBV. Simeprevir combined with PEG-IFN/RBV provided HCV elimination in more patients than did the combination of placebo with PEG-IFN/RBV (SVR12 rate: 81% *vs* 50%, $P < 0.001$). The relapse rate in the simeprevir/PEG-IFN/RBV arm was lower than that in the placebo/PEG-IFN/RBV arm (13% *vs* 24%), as was the rate of treatment failure (7% *vs* 32%). The QUEST-2 study showed that simeprevir 150 mg/d OD given along with PEG-IFN/RBV provides a high SVR12 rate, making it possible to decrease the treatment duration to 24 wk in a majority of patients (91%).

The objective of the phase Ⅲ trial PROMISE (TMC435-HPC3007) was to study the efficacy, safety and tolerability of simeprevir combined with PEG-IFN/RBV in patients infected with genotype 1 HCV and treatment failure. The study enrolled 393 prior relapsers after treatment. Approximately 40% of patients had the 1a subtype of the HCV genotype, approximately 75% of them had the unfavorable genotype IL28B, 15% had considerable liver fibrosis (stage F3), and 15% had diagnosed liver cirrhosis (stage F4). Patients were given 150 mg of simeprevir combined with PEG-IFN/RBV for 12 wk, followed by PEG-IFN/RBV only for another 12 wk. At this point, the patients either stopped treatment based on the RGT criteria (no virus in blood at treatment week 4 and 12) or continued PEG-IFN/RBV treatment up to week 48. In the control arm, placebo combined with PEG-IFN/RBV was given for 12 wk; up to week 48, they were given basic treatment, *i.e.,* PEG-IFN/RBV. A total of 77% of the simeprevir-treated patients and 3% of the control group developed rapid treatment response in 4 wk (RVR). At the end of treatment, the responses were very high: 97% in the simeprevir group and 72% in the control. The majority of patients (93%) complied with the RGT criteria (treatment termination at week 24); in this group, 83% of patients reached SVR during the following 12 wk of basic treatment (SVR12). Among the remaining 7% of simeprevir-treated patients who did not comply with the RGT criteria and continued treatment to week 48, SVR12 was reached in only 32%. Among patients with HCV subtype 1a, SVR12 was reached in 70% of the simeprevir-treated group and in 28% of the placebo group; for subtype 1b, these values were 86% and 43%, respectively. The IL28B CC genotype was associated with a better response to simeprevir-based triple therapy *vs* control (SVR12 was 89% *vs* 53%). SVR12 for the CT genotype was 79% *vs* 34%. SVR12 for the TT genotype was 65% *vs* 19%. Regardless of fibrosis severity, the SVR rate in the simeprevir-treated arms was higher than in control. For instance, with fibrosis stage F0-F2 (absent to moderate), the SVR rate was 82%; with significant fibrosis, it was 73%; and with liver cirrhosis, it was 74%. In the control group, SVR reached 41%, 20% and 26%, respectively. Ineffective treatment was noted in 3% of simeprevir-treated patients and in 27% of control patients. Relapse after treatment completion was found in 19% and 48%, respectively. Thus, in case of relapse after conventional therapy with PEG-IFN/RBV in genotype 1 HCV patients, treatment with simeprevir and PEG-IFN/

RBV provided a high cure rate: 79% of patients reached SVR12.

The phase Ⅲ trial ATTAIN (NCT01485991) is studying the efficacy of simeprevir plus PEG-IFN/RBV and telaprevir plus PEG-IFN/RBV in patients with a failed attempt at HCV eradication after conventional therapy (PEG-IFN/RBV). ATTAIN is projected to be finished in 2014.

Safety

The profile of adverse events recorded in the PILLAR study[15,16] was similar between the group treated with simeprevir and the group with conventional treatment. For instance, comparing patients treated with simeprevir/PEG-IFN/RBV *vs* placebo/PEG-IFN/RBV, an adverse event rate > 10% was recorded for fatigue (42.4% and 48.1%, respectively), flu-like syndrome (31.7% and 37.7%, respectively), itching (31.1% and 45.5%, respectively), headache (46.0% and 51.9%, respectively), nausea (27.8% and 27.3%, respectively), rash (21.0% and 23.4%, respectively), anemia (20.4% and 20.8%, respectively), neutropenia (24.3% and 20.8%, respectively).

The majority of adverse events recorded in patients treated with simeprevir/PEG-IFN/RBV in the ASPIRE study were also observed in patients treated with disease-modifying therapy PEG-IFN/RBV (fatigue, flu-like syndrome, itching, headache, nausea) and were similar to the patient control group[17,18]. Adverse events requiring the discontinuation of at least one of the therapeutics in the study were reported in 4%-10.4% of the patients treated with simeprevir/PEG-IFN/RBV combination compared to 13% of the control group. Serious adverse events (SAEs) were detected at similar rates in patients treated with the combination of simeprevir and disease-modifying therapy (3.8%-11.5%) and in the patients treated with placebo combined with disease-modifying therapy (13%). Anemia developed in 19.0%-22.1% of patients treated with simeprevir + PEG-IFN/RBV and in 20.8% of patients treated with placebo combined with PEG-IFN/RBV. In both arms, anemia did not result in discontinued treatment. Skin rash of any type was reported in 23.4%-30.8% of patients treated with simeprevir + PEG-IFN/RBV and in 20.8% of in patients treated with placebo + PEG-IFN/RBV. Rash resulting in discontinued treatment was noted in only 3 cases (2 patients of the simeprevir + PEG-IFN/RBV arm and 1 patient of the placebo + PEG-IFN/RBV arm). Insignificant, isolated and reversible increase of both bilirubin types (direct and indirect) in blood serum was found in patients treated with simeprevir + PEG-IFN/RBV. Because elevated plasma activity of alanine aminotransferase (ALT) and alkaline phosphatase (ALP) was not associated with the simultaneous elevation of bilirubin, the elevated serum ALT in the majority of patients was interpreted as a developed biochemical response during the treatment.

In the PILLAR and ASPIRE studies, fatigue as a treatment-related adverse event was reported in 63%-65% of treatment-naive and 97% of treated patients[21,22]. In both trials, fatigue severity according to the Fatigue Severity Scale increased with treatment duration. However, fatigue disappeared more quickly in treatment-naive simeprevir-treated patients than it did in patients treated with PEG-IFN/RBV only. Considering the follow-up period of 72 wk after treatment completion, these differences were statistically significant ($P < 0.001$).

These trials also showed lower the quality of life in patients according to the health-related quality of life (HRQoL) scale. Treatment-naive simeprevir-treated patients showed a faster quality of life improvement compared to the group treated with PEG-IFN/RBV only[21,22].

Simeprevir was well tolerated by patients enrolled in the QUEST-1, QUEST-2, and PROMISE studies[19-23]. The total AE incidence was similar in the arms treated with simeprevir + PEG-IFN/RBV and placebo + PEG-IFN/RBV.

Discontinued treatment due to adverse events in both arms was found in 3% of patients[19]. The grade 3-4 adverse event rate was 23% in the simeprevir + PEG-IFN/RBV patient arm and 29% in the PEG-IFN/RBV arm. The most common adverse events in the simeprevir and placebo arms were fatigue (40% and 38%, respectively), headache (31% and 37%, respectively), and itching (21% and 11%, respectively). Simeprevir intake was associated with transient moderately elevated bilirubin that was not associated with elevated aminotransferases or alkaline phosphatase. Rash and photosensitivity were slightly more common in patients who were treated with simeprevir compared to the patients receiving placebo (27% *vs* 20% and 4% *vs* 1%, respectively). During the PROMISE study, a shorter treatment duration resulted in lower fatigue intensity and a faster return to normal activity among patients treated with simeprevir and PEG-IFN/RBV.

Summary

Simeprevir seems to be preferable when choosing HCV treatment compared to telaprevir or boceprevir because it is advantageous with regard to dosing regimen (once a day), tolerance and safety (no rash or anemia). All three phase Ⅲ trials, QUEST-1, QUEST-2, and PROMISE, showed a high infection cure rate (79%-81% SVR12). Importantly, the addition of simeprevir to PEG-IFN/RBV was associated with a higher SVR rate without a significant increase in fatigue severity or decrease in quality of life. Moreover, the shorter-duration antiviral treatment with simeprevir was associated with a higher SVR rate and a shorter period of worsened quality of life.

FALDAPREVIR

Faldaprevir (BI 201335, Boehringer Ingelheim Pharmaceuticals, Ingelheim, Germany) is a 2nd-generation NS3/4A protease inhibitor with once-a-day dosing.

Efficacy

Faldaprevir's efficacy, tolerance and safety were studied

in genotype 1 HCV patients in multiple phase Ⅱ and Ⅲ clinical trials (SILEN-C1, SILEN-C2, SILEN-C3, STARTVerso™1).

SILEN-C1 and SILEN-C2 were phase Ⅱ randomized clinical studies with the objective of examining BI 201335's efficacy and safety in combination with PEG-IFN/RBV in treatment-naive patients[22] and in treatment failures (partial or non-responders)[24] infected with genotype 1 HCV. Both trials studied the effectiveness of a 3-d lead-in phase with PEG-IFN/RBV. The lead-in period was used when studying boceprevir's efficacy in combination with PEG-IFN/RBV in genotype 1 HCV patients[13,25]. This treatment phase was expected to lower the probability of developing HCV resistance during the treatment.

SILEN-C1 enrolled 429 treatment-naive patients infected with genotype 1 HCV[22]. Four study arms were made: for 24 wk, patients were administered a combination of PEG-IFN/RBV with placebo (control group), faldaprevir 120 mg OD with a 3-d PEG-IFN/RBV lead-in (LI) phase, faldaprevir 240 mg OD with LI, or faldaprevir 240 mg OD without LI followed by PEG-IFN/RBV therapy up to the total 24 wk. If a patient taking faldaprevir 240 mg complied with the RGT criteria (HCV RNA < 25 IU/mL at week 4, undetectable viral load at weeks 8-20), the treatment was discontinued at week 24. The rest of the patients continued PEG-IFN/RBV therapy up to week 48. The SVR rate was 56%, 72%, 72% and 84%, respectively, for the four arms. In total, 92% of patients with the RGT in the faldaprevir 240 mg OD arms reached SVR, irrespective of the PEG-IFN/RBV duration, and 82% of patients with genotype 1a treated with faldaprevir 240 mg OD reached SVR, compared to 47% in the placebo group.

SILEN-C2 enrolled 288 patients without liver cirrhosis who were partial or null-responders to previous HCV treatment[24]. All three arms were treated with faldaprevir combined with PEG-IFN/RBV for 48 wk: 240 mg OD with a 3-d PEG-IFN/RBV lead-in, 240 mg OD without LI, or 240 mg BID with LI. Patients treated with faldaprevir 240 mg OD/LI and reaching HCV RNA < 25 IU/mL by week 4 and undetectable HCV at weeks 8-20 were randomized again. Some of them stopped treatment at week 24, and the others continued PEG-IFN/RBV therapy up to week 48. The SVR rate in prior partial responders was 32%, 50% and 42% in the arms given faldaprevir 240 mg OD with LI, faldaprevir 240 mg OD without LI, and 240 mg BID with LI, respectively. The SVR rate in prior null responders was 21%, 35% and 29% in the respective arms. In patients given faldaprevir 240 mg OD with lead-in (LI) and an AVT duration of 24 wk, the percentage of patients with RGT who reached SVR24 was 43%, while in those continuing treatment up to week 48 it was 72% ($P = 0.035$).

Summarizing the results of these two trials, we should note that due to unclear reasons, the patient arms treated with a 3-d lead-in phase (lead-in arms) experienced a treatment effectiveness that was significantly lower, which was a basis for refusing such management to limit the chances of developing faldaprevir resistance.

SILEN-C3 enrolled 159 treatment-naive patients with genotype 1 HCV. Patients were randomized into two arms: 12 and 24 wk of treatment with 120 mg of BI 201335 OD combined with PEG-IFN/RBV. Liver cirrhosis was found in approximately 12% of patients at treatment onset; 48% of the first arm patients and 37% of the second arm patients had subtype 1a HCV, and 46% and 53%, respectively, had subtype 1b HCV. Both patient arms had a lead-in period of 3 d of PEG-IFN/RBV prior to starting BI 201335 therapy. Patients with an early rapid virologic response (eRVR), meaning unquantifiable HCV RNA at week 4 and undetectable load at weeks 8-18, stopped therapy. The rest of the patients continued treatment with PEG-IFN/RBV only up to week 48. SVR rates were similar for both AVT types (65% *vs* 73%) and in patients with eRVR (82% *vs* 81%).

The STARTVerso™ (placebo-controlled, double blinded, phase Ⅲ) trial studied the efficacy and safety of faldaprevir combined with PEG-IFN/RBV in 652 patients previously not treated with AVT and with HCV subtypes 1a and 1b, including patients with compensated liver cirrhosis[26]. The patients were divided into three arms: placebo combined with PEG-IFN/RBV for 24 wk, faldaprevir 120 mg OD combined with PEG-IFN/RBV for 12 or 24 wk (RGT arm), and faldaprevir 240 mg OD combined with PEG-IFN/RBV for 12 wk. Patients complying with the RGT criteria (HCV RNA < 25 IU/mL at week 4 and undetectable load at week 8) and treated with faldaprevir combined with PEG-IFN/RBV stopped treatment at week 24. Patients who did not comply with the RGT criteria who were treated with placebo/PEG-IFN/RBV were given PEG-IFN/RBV treatment only up to week 48. The primary endpoint was reaching SVR within 12 wk of the planned treatment completion (SVR12). Patients given faldaprevir OD in combination with PEG-IFN/RBV (120 and 240 mg) reached SVR12 in 79% and 80% of cases, respectively. Compared with these 2 arms, the placebo/PEG-IFN/RBV arm had a SVR12 rate of 52% ($P < 0.0001$). In the RGT arm, early rapid response was seen in 87% and 89% of faldaprevir-treated patients (120 and 240 mg, respectively). Those patients were fully compliant with the criteria for treatment shortening. Treated for 12 wk with faldaprevir and 24 wk with PEG-IFN/RBV alone, 86% and 89% of this patient arm (120 and 240 mg, respectively) reached SVR12. Thus, the STARTVerso™ trial showed that it is possible for a majority of patients (88%) to shorten the treatment to 24 wk with considerable HCV elimination compared to patients treated with PEG-IFN/RBV only for 48 wk.

Safety

All phase Ⅱ studies of the SILEN-C series reported that the differences in AE patterns and rates were not significant, including rash, photosensitivity, nausea, vomiting and diarrhea. As in the trials of other PIs, faldaprevir for HCV treatment was associated with transitory elevation

of non-conjugated bilirubin. With a faldaprevir OD regimen, significant AEs developed less frequently compared to a BID regimen.

In the phase Ⅲ trial STARTVerso™[26], all drugs were discontinued in 4% of patients in the placebo arm, 4% in the faldaprevir 120 mg arm, and 5% in the faldaprevir 240 mg arm. Faldaprevir only was discontinued in 1% of patients in the 120 mg arm and 3% in the 240 mg arm. Serious adverse events developed in in 6%, 7% and 7% of patients in the respective study arms. Grade 3 rash (severe) was reported in < 1% in each of the study arms. The rate of Hb drop within first 24 wk (Hb ⩽ 8.5 g/dL) was similar in all arms (2%, 3% and 3%, respectively).

Summary

Faldaprevir OD combined with PEG-IFN/RBV provides a high SVR rate in HCV patients along with good tolerance and safety.

DANOPREVIR

Danoprevir (RG7277; Roche, Basle, Switzerland; InterMune Pharmaceuticals, Brisbane, CA, United States) is a 2nd-generation NS3/4A protease inhibitor of macrocyclic origin with the same activity toward HCV genotypes 1, 4 and 6 (*in vitro*)[27,28]. Phase I clinical studies showed the high antiviral activity of danoprevir for genotype 1 HCV. Danoprevir in that category of patients was administered as monotherapy, combined with PEG-IFN/RBV, or combined with a HCV polymerase inhibitor, *i.e.*, mericitabine, in an interferon-free regimen[29-32].

Efficacy

The phase Ⅱ trial DAUPHINE[33] studied the efficacy of three danoprevir doses (50, 100 and 200 mg) boosted with ritonavir 100 mg taken BID in combination with PEG-IFN/RBV (RGT). Ritonavir addition is known to increase the PI blood concentration, thereby suppressing CYP3A activity. Twelve weeks after treatment completion, the SVR12 rate was 93% in genotype 1 HCV patients treated with danoprevir 200 mg BID combined with PEG-IFN/RBV. Danoprevir 100 mg/d provided a SVR12 rate of 83%, and 50 mg/d 67%. The effectiveness of danoprevir 200 mg BID combined with PEG-IFN/RBV was not affected by HCV genotype subtype (1a *vs* 1b) or *IL28B* genotype (CC *vs* non-CC).

The objective of the randomized, placebo-controlled, parallel-group phase Ⅱ trial ATLAS (NCT00963885) was to study the efficacy and safety of RGT danoprevir combined with PEG-IFN/RBV for 12 wk compared to PEG-IFN/RBV in naive genotype 1 HCV patients[34]. It was an international study, with sites in North America (31 sites), Europe (8 sites) and Australia (3 sites). Patients who had not previously been treated for HCV (treatment-naïve patients) were randomized into 4 groups. For 12 wk, patients were given danoprevir (300 mg every 8 h, 600 mg every 12 h or 900 mg every 12 h) or placebo in combination with PEG-IFN/RBV. Follow-up treatment included PEG-IFN/RBV therapy only. Patients with an extended rapid virologic response (eRVR) (RNA < 15 IU/mL for 4-20 wk) stopped treatment at week 24. Patients without eRVR continued PEG-IFN/RBV therapy for 48 wk. The main criterion for assessing efficacy was SVR within 24 wk after treatment completion. The SVR rate was 68% in patients treated with danoprevir 300 mg, 85% in danoprevir 600 mg and 76% in danoprevir 900 mg, compared with 42% in placebo-treated patients. RGT was found in 71 patients given danoprevir 600 mg combined with PEG-IFN/RBV, and SVR was found in 96%.

Safety

In the ATLAS study, serious adverse events were reported for 7%-8% of danoprevir-treated patients and for 19% of placebo-treated patients. Four danoprevir-treated patients had transient ALT elevation. The highest danoprevir dose (900 mg) resulted in grade 4 ALT elevation that, in turn, required therapy discontinuation in the relevant patient arm.

Summary

Danoprevir combined with PEG-IFN/RBV resulted in a high SVR rate in genotype 1 HCV patients. However, high danoprevir doses can result in prominent ALT elevation requiring AVT discontinuation.

ASUNAPREVIR

One of the most considerable achievements in AVT development with PI combinations (if not the most important) is the phase Ⅱa trials with asunaprevir (ASV, BMS-650032, 600 mg; BID) and daclatasvir (DCV, NS5A inhibitor, 60 mg; OD) combined with conventional therapy and a comparison group (with no conventional treatment).

Efficacy

A phase Ⅱ CT with the above combination, the AI447-011 study, showed its efficacy for one of the most complex HCV-infected patient groups: non-responders with zero prior virologic response (HCV RNA decreased less than 2 $\log_{10}$ by week 12 of conventional therapy). This group appears to be the most complex from the point of view of antiviral regimen selection because null responders should be considered insensitive to IFN-based agents. That study's results show that a combination of direct-acting antivirals is the only therapeutic option for this patient category. The design of the AI447-011 study involved an efficacy comparison in 2 patient arms: Arm 1 was given the combination of ASV + DCV, and arm 2 was given ASV+ DCV + conventional therapy. The treatment duration was 24 wk; one of the important exclusion criteria was liver cirrhosis[35] (Figure 4). The study reported the seemingly unreachable SVR of 90% among null responders under complex therapy (ASV+ DCV + conventional therapy).

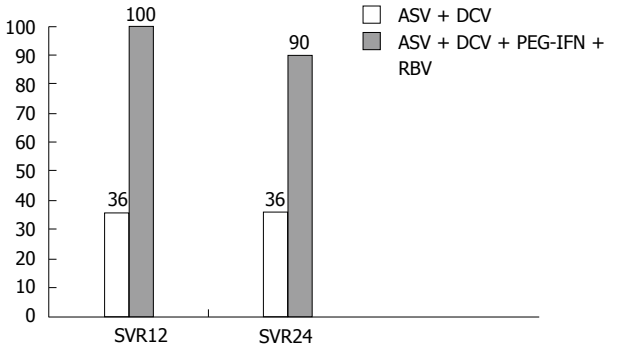

Figure 4 Asunaprevir rate (%) after 12- and 24-wk follow-up in the AI447-011 study. ASV: Asunaprevir; DCV: Daclatasvir; PEG-IFN: PEG-IFNPE-Gylated interferon; RBV: Ribavirin.

Table 7 Effectiveness of combined therapy with asunaprevir *n* (%)

	Null response (*n* = 21)	Contraindications to IFN-based therapy (*n* = 22)
RVR4	20 (95.2)	15 (68.2)
RVR12	19 (90.5)	14 (63.6)
SVR24	19 (90.5)	14 (63.6)

Data of BMS CT, Suzuki *et al*[36], 2012. IFN: Interferon.

Even more impressive results were shown by Japanese researchers, Suzuki *et al*[36] (2012), who also used an ASV + DCV regimen in null-responders (*n* = 21); their comparison group included patients (*n* = 22) with contraindicated IFN-based therapy (Table 7). Their data showed an SVR of 90.5% in group 1. Additionally, this CT showed the prognostic value of EVR: all EVR patients reached SVR.

The study of the ASV + DCV combination drew the following conclusions: *IL28B* polymorphism appears to lose its SVR predictive value; the majority of patients with aviremia after 2 wk treatment had the CC-genotype, without significant SVR differences in patients with different *IL28B* genotypes (Figure 5).

Safety

The study of the ASV+DCV combination reported relatively more often AEs related to moderate headache, nasopharyngitis exacerbation elevated aminotransferases, and diarrhea. Laboratory AEs were moderate and severe [grade 3-4 (G3-4)] impairments related to elevated transaminase activity. Serious adverse events were found in 6 patients: mild and moderate pyrexia (G2-3), moderate gastroenteritis (in 2 patients); hyperbilirubinemia (G4). In all patients pyrexia disappeared in 4 to 10 d after AVT cancellation. Hyperbilirubinemia and cytolytic syndrome resolved within 4 wk after treatment discontinuation (Table 8). We should note that in the studies of ASV + DCV + conventional therapy combinations, the AE structure showed a prevalence of disorders caused by conventional treatment.

Summary

Asunaprevir-based AVT regimens are highly effective (above 90%) in the most challenging patient category (null responders); the safety profile of the given AVT regimen was mainly not different from PEG-IFN/RBV.

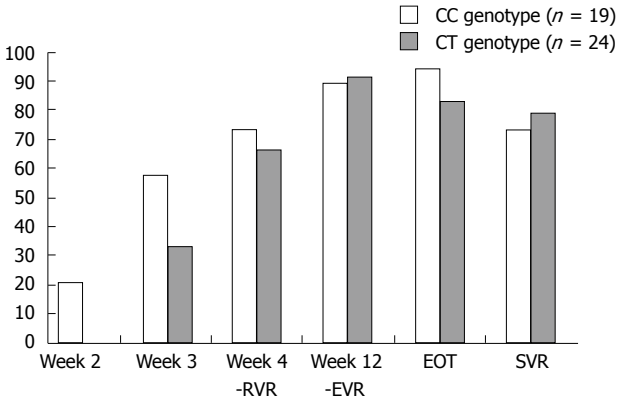

Figure 5 Undetectable hepatitis C virus RNA rate depending on *IL28B* polymorphism.

Table 8 Adverse event structure for asunaprevir

	Lok *et al*[35] AI447-011		Suzuki *et al*[36]	
	ASV + DCV + conventional therapy (*n* = 10)	ASV + DCV (*n* = 11)	Null response (*n* = 21)	Contraindications to IFN-based therapy (*n* = 22)
Diarrhea	70.0%	72.7%	43%	9%
Fatigue	70.0%	54.5%	-[1]	-[1]
Headache	50.0%	45.5%	38%	27%
Nausea	50.0%	18.2%	-[1]	-[1]
Coughing	20.0%	27.3%	-[1]	-[1]
Subfebrile temperature	27.3%	10.0%	14%	23%

[1]Adverse events are not shown because they were observed in fewer than 3 patients. AE: Adverse event; ASV: Asunaprevir; DCV: Daclatasvir; IFN: Interferon.

ABT-450

Agent ABT-450 (AbbVie) is used only in combination with the non-nucleoside inhibitor NS5B (ABT-333), ribavirin and ritonavir. Therefore, ABT-450 efficacy and safety should be considered only a multicomponent "achievement".

Efficacy

The clinical efficacy of an ABT-450-based AVT treatment was published as the results of the AVIATOR study, a phase Ⅱa CT, by Poordad *et al*[37] (2013). The genotype 1 patient population mainly included treatment-naive patients (66%, *n* = 33), while partial responders and null responders comprised 34% of the population (*n* = 17). ABT-450 was not used as monotherapy. The dosing of the inhibitor combination depended on the studied population. The given study used a combination of NS5B (ABT-333), ribavirin and ritonavir coupled with various ABT-450 doses for 12 wk. The results showed that ABT-450 was effective at 150 mg OD: the SVR rate

Table 9 AVIATOR, phase Ⅱa study (combination of ABT-450 + ritonavir + ABT-333 + ribavirin)

Study arm	*n*	Genotype	Status	Combination	Duration	Treatment regimen	SVR
Total: group 1 + 2	33	1a/1b (28/5)	Naive	ABT-450 + ritonavir + ABT-333 + ribavirin	12 wk	ABT-450, 250 mg/d or 150 mg/d + ritonavir, 100 mg/d; ABT-333, 400 mg BID; ribavirin, body weight-based	93%-95%
3	17	1a/1b (16/1)	partial virologic response, null response	ABT-450 + ritonavir + ABT-333 + ribavirin	12 wk	ABT-450, 150 mg/d; ritonavir, 100 mg/d; ABT-333, 400 mg BID; ribavirin, body weight-based	47%

Table 10 SVR rate depending on *IL28B* polymorphism

Study arm	Status	CC-genotype	CT-genotype	TT-genotype	SVR
1	Naive	10/9	7/7	2/2	95%
2	Naive	5/4	7/7	2/2	93%
3	Partial virologic response, null response	0/0	12/6	5/2	47%

Table 11 Adverse event incidence of ABT-450 + ritonavir + ABT-333 + ribavirin combination

AEs with incidence above 20%	AE incidence
Headache	14%-26%
Fatigue	35%-47%
Insomnia	0-26%
Nausea	21%-24%
Rash	6%-21%

AE: Adverse event.

amounted to 93%, compared to 95% in the comparison group with ABT-450 250 mg OD (Table 9). The phase Ⅱb study of the combination (2013) showed comparable efficacy in similar study arms: treatment-naive 89% and 96%, null responders 89 and 95%, respectively. It should be noted that the SVR rate for ABT-450-based AVT did not depend on *IL28B* polymorphism (Table 10).

Safety

There were no noted specific AEs from ABT-450-based AVT. The most common were headache, fatigue, nausea (Table 11). However, good tolerance in its totality is related not only to ABT-450 but also to other combination constituents[38]. It is worth mentioning that despite the presence of ribavirin in the combination, anemia was not a frequent AE deserving special attention.

Summary

ABT-450 + ritonavir + ABT-333 + ribavirin in phase Ⅱa and Ⅱb studies was highly effective in HCV patients with the following criteria: genotype 1, both treatment-naive patients and null responders, no liver cirrhosis. At the moment, studies for optimal treatment duration are ongoing. Regarding safety, this combination was well tolerated, and possible AEs were mostly related to asthenia syndrome. Specific AEs were not detected in the studies.

Table 12 SVR rate in genotype 1 hepatitis C virus patients *n* (%)

	GS-9256 + tegobuvir (*n* = 15)	GS-9256 + tegobuvir + ribavirin by weight (*n* = 13)	GS-9256 + tegobuvir + ribavirin by weight + PEG-IFNα (*n* = 14)
Week 4, RVR	1/15 (7)	6/13 (46)	10/14 (71)
Week 12, EVR	3/15 (20)	8/13 (62)	14/14 (100)
Week 24, SVR	10/15 (67)	13/13 (100)	13/14 (94)

PEG-IFNα: PEGylated interferon-α.

GS-9256

GS-9256 was used only in combination with the non-nucleoside inhibitor tegobuvir (GS-9190). Therefore, GS-9256's efficacy and safety should be considered only in a multicomponent treatment.

Efficacy

Another representative of the PI class, GS-9256 (Gilead) was studied in combination with the non-nucleoside inhibitor tegobuvir (GS-9190) and ribavirin. The combination of 4 agents (GS-9256 + tegobuvir + ribavirin + PEG-IFNα) was used as a comparison group. According to the phase Ⅱ study by Zeuzem *et al*[39] (2010), the SVR rate was comparable in the absence vs. the presence of PEG-IFNα: 100% *vs* 94%. The SVR rate of the two-component regimen (only with direct-acting antivirals) amounted to 67% (Table 12).

Safety

Patients taking GS-9256 + tegobuvir 40 mg showed good tolerance, and the majority of AEs were of medium severity. No specific AEs were found. Conversely, the comparison arm (GS-9256 + tegobuvir + ribavirin by weight + PEG-IFNa) developed common AEs typical for PEG-IFN/RBV regimens (Table 13). During the CT period, 2 cases of serious AEs were reported: bursitis (infected) and vasovagal attack, which the investigators interpreted as not related to the studied agent. No laboratory impairments of serious AE (G4) type were found.

Summary

In general, GS-9256 + tegobuvir + ribavirin is highly effective in treatment-naive genotype 1 HCV patients. An analysis of the phase Ⅱ study results indicated a good safety profile for combinations including GS-9256.

Table 13 Most common adverse event after 4 treatment weeks

	GS-9256 + tegobuvir	GS-9256 + tegobuvir + ribavirin by weight	GS-9256 + tegobuvir + ribavirin by weight + PEG-IFN[1]
AE incidence	50%	93%	81%-100%
Anemia	0	0	0-13%
Eye pain	0	0	0-13%
Diarrhea	19%	20%	6%-40%
Nausea	13%	20%	6%-40%
Flu-like syndrome	0	0	44%-80%
Fatigue	6%	33%	13%-33%
Headache	31%	47%	13%-40%
Insomnia	0	20%	6%-13%
Dry skin	0	13%	0%
Pruritus	6%	20%	0%-7%

[1]Mean value of two CT phases. AE: Adverse event; PEG-IFN: PEGylated interferon.

CONCLUSION

The appearance in clinical settings of the first direct-acting antivirals to treat HCV provided improved effectiveness and decreased AVT duration in a majority of genotype 1 patients.

The addition of protease inhibitors has been beneficial for HCV patients. The SVR rate of 40%-50% obtained using conventional treatment was significantly improved (up to 80%) through the addition of telaprevir or boceprevir in triple therapy regimens with the provision that AVT is administered following all main approaches and principles (*e.g.*, accounting for contraindications, potential drug-drug interactions, adherence to AVT regimens depending on initial patient parameters)[10].

Another solid argument for the development of new combined regimens that include direct-acting antivirals is the high rate of hematological AEs, especially ribavirin-induced anemia. When new AVTs for genotype 1 HCV are introduced, most attention should be paid to the regimens, such as by excluding PEG-IFNα to expand the treatment groups and including patients with contraindications to IFN and IFN intolerance.

Our review shows that combinations of direct-acting antivirals can become a novel therapeutic standard not only for patients with contraindicated IFN therapy. PI combinations with other direct-acting antivirals can improve the SVR rates in non-responders with prior partial virologic response and, more importantly, in those with prior null virologic response (Table 14).

When triple therapy appeared, it was the only combination available for null responders. However, the evident barriers were interferon intolerance and issues with concomitant treatment selection to avoid drug interactions. Currently, asunaprevir-based combinations are the treatment of choice for null responders. They have a SVR rate of 90%, and in case of interferon intolerance, patients can be offered antiviral ABT-450-based regimens. In any case, the era of direct-acting antivirals assumes interferon-free therapy. Once, supposedly ideal regimens for HCV treatment implied interferon-free combinations. Now, the emergence of direct-acting antivirals makes it possible to develop optimally dosed treatments and completely exclude clinically significant AEs related to interferon use.

Table 14 SVR dependence in null responders for various direct-acting antiviral combinations

Ref.	*n*	Combination	Duration	SVR
Zeuzem *et al*[39]	37	Telaprevir-based triple therapy	48 wk	33%
Bacon *et al*[25]	58	Boceprevir-based triple therapy	48 wk	52%
Lok *et al*[35]	11	DCV + ASV	24 wk	36%
Lok *et al*[35]	10	DCV + ASV + conventional therapy	24 wk	90%
Suzuki *et al*[36]	21			
Poordad *et al*[37]	7	ABT-450 + ritonavir + ABT-333 + ribavirin	12 wk	43%

DCV: Daclatasvir; ASV: Asunaprevir.

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P- Reviewers: Liu J, Takaguchi K, Tziomalos K **S- Editor**: Qi Y
L- Editor: A **E- Editor**: Wang CH

World Journal of Hepatology

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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4254/wjh.v6.i5.340

World J Hepatol 2014 May 27; 6(5): 340-346
ISSN 1948-5182 (online)

RESEARCH REPORT

CYP2E1 immunoglobulin G4 subclass antibodies after desflurane anesthesia

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Received: November 2, 2013 Revised: January 20, 2014
Accepted: March 3, 2014
Published online: May 27, 2014

Abstract

AIM: To investigate CYP2E1 IgG4 autoantibody levels and liver biochemical markers in adult patients after anesthesia with desflurane.

METHODS: Forty patients who were > 18 years old and undergoing elective surgery under general anesthesia with desflurane were studied. Alpha-glutathione-S-transferase (αGST) and IgG4 antibodies against CYP2E1 were measured preoperatively and 96 h postoperatively, as well as complete blood count, prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR), aspartate aminotransferase (SGOT), alanine aminotransferase (SGPT), g-glutamyl-transpeptidase (gGT), alkaline phosphatase, total serum proteins, albumin and bilirubin. A separate group of 8 patients who received regional anesthesia was also studied for calibration of the methodology used for CYP2E1 IgG4 and αGST measurements. Student's t-test and the Mann-Whitney *U* test were used for comparison of the continuous variables, and Fisher's exact test was used for the categorical variables. All tests were two-tailed, with statistical significance set as $P < 0.05$.

RESULTS: None of the patients developed postoperative liver dysfunction, and all patients were successfully discharged from the hospital. No statistically significant difference was observed regarding liver function tests (SGOT, SGPT, γGT, bilirubin, INR), αGST and CYP2E1 IgG4, before and after exposure to desflurane. After dividing patients into two subgroups based on whether or not they had received general anesthesia in the past, no significant difference in the levels of CYP2E1 IgG4 was observed at baseline or 96 h after desflurane administration ($P = 0.099$ and $P = 0.051$, respectively). Alpha-GST baseline levels and levels after the intervention also did not differ significantly between these two subgroups ($P > 0.1$). The mean αGST differences were statistically elevated in men by 2.15 ng/mL compared to women when adjusted for BMI, duration of anesthesia, number of times anesthesia was administered previously and length of hospital stay. No significant difference was observed between patients who received desflurane and those who received regional anesthesia at any time point.

CONCLUSION: There was no difference in CYP2E1 IgG4 or αGST levels after desflurane exposure; further

research is required to investigate their role in desflurane-induced liver injury.

Key words: Drug-induced-liver injury; Desflurane; Anesthesia; Hepatotoxicity; CYP2E1 IgG4

Core tip: Several case reports of hepatotoxicity following anesthesia with desflurane have been published in the literature, implicating cytochrome P450 2E1-IgG4 autoantibodies. This study investigates the possible changes in CYP2E1 IgG4 autoantibody levels and other biochemical markers of liver injury in 40 adult patients who received anesthesia with desflurane for elective surgery. Samples were obtained before and 96 h after exposure to desflurane, and no significant difference was observed in levels of CYP2E1 IgG4, a-glutamyl-S-transferase, aspartate aminotransferase, alanine aminotransferase, g-glutamyl-transpeptidase or alkaline phosphatase levels, regardless of patients' previous exposure to volatile anesthetics.

Batistaki C, Michalopoulos G, Matsota P, Nomikos T, Kalimeris K, Riga M, Nakou M, Kostopanagiotou G. CYP2E1 immunoglobulin G4 subclass antibodies after desflurane anesthesia. *World J Hepatol* 2014; 6(5): 340-346 Available from: URL: http://www.wjgnet.com/1948-5182/full/v6/i5/340.htm DOI: http://dx.doi.org/10.4254/wjh.v6.i5.340

INTRODUCTION

Volatile anesthetics, mostly halothane, have been implicated as causative agents of drug-induced liver injury (DILI)[1-5], which has been reported to occur in approximately 1 out of 10000 adult patients receiving general anesthesia with halothane[4,5]. Three main mechanisms have been implicated in the development of hepatotoxicity: (1) a hypersensitivity reaction; (2) the production of hepatotoxic metabolites; and (3) hypoxia[4]. A hypersensitivity reaction is believed to be the most important of these mechanisms, it is also known as idiosyncratic drug-induced hepatitis (IDDIH) and is caused by the production of trifluoroacetylated (TFA) hepatic proteins during the metabolism of halothane by the cytochrome P450 2E1 (CYP2E1)[4]. These proteins act as neoantigens and are responsible for the production of autoantibodies against liver tissue[6-8]. In 1996, it was demonstrated that autoantibodies that react with CYP2E1 were significantly elevated in 45%-70% of patients with halothane hepatitis[7,9], particular including CYP2E1 IgG4 and 58 kDa endoplasmic reticulum protein (ERp58) autoantibodies[10,11].

With the development of newer volatile anesthetics, the risk of developing DILI has decreased, mainly due to the reduced metabolism of newer agents by CYP450 2E1 (20%-30% for halothane, compared to 2% for enflurane, 1% for sevoflurane, 0.2%-0.6% or less for isoflurane and 0.02% for desflurane)[12,13]. Njoku *et al*[14] (1997) demonstrated that desflurane produces lower levels of TFA hepatic proteins, reflecting the decreased metabolism of the agent by CYP2E1. Despite the fact that desflurane seems to have the best safety profile in this regard and is believed to have minimal, if any, hepatotoxic effect, there have been several case reports published implicating desflurane as a causative agent of DILI[11,15-20].

Aspartate aminotransferase (SGOT), alanine aminotransferase (SGPT), g-glutamyl-transpeptidase (gGT), alkaline phosphatase (ALP), albumin, bilirubin and coagulation status are all classical biochemical markers of liver injury, and they have all been reported to change significantly in all published case reports of hepatocellular damage due to desflurane anesthesia[11,15-20]. Additionally, alpha-glutathione S-transferase is believed to be a sensitive marker of hepatocellular injury because it is distributed equally in centrilobular and periportal hepatocytes, in contrast to SGOT/SGPT[21,22]. This distribution is important because liver biopsies of patients with halothane hepatitis have demonstrated that the main histological characteristic of this condition is centrilobular hepatic necrosis[4].

Based on case reports of desflurane hepatotoxicity and the possible mechanisms of DILI in the case of volatile anesthetics, the aim of this study was to investigate the possible production or alteration of CYP2E1 IgG4 autoantibody levels in addition to other biochemical markers of liver injury in patients who received general anesthesia with desflurane.

MATERIALS AND METHODS

The Institutional Review Board and Ethics Committee of "Attikon" University Hospital, where the study was conducted, approved the study, and written informed consent was obtained from all patients. Forty randomly selected adult patients who had received general anesthesia with desflurane for elective surgery between 01/2008 and 07/2011 were included. The exclusion criteria included the following: age < 18 years old; American Society of Anesthesiologists classification > Ⅲ; history of liver disease of any etiology; history of chronic hepatitis B or C, recent viral disease of unknown etiology; history of exposure to hepatotoxic doses of acetaminophen, nonsteroidal anti-inflammatory drugs or antiepileptic drugs; current treatment with hepatotoxic drugs or immunosuppressants; autoimmune or connective tissue disorders; history of alcohol or illicit drug use; pregnancy; malignancies; intra-abdominal procedures; and operating time of more than 6 h.

Patients' complete medical history and medications were recorded during preoperative assessment. Samples of serum were collected from all patients preoperatively, immediately postoperatively and every 24 h until the 4th postoperative day (96 h after the completion of the surgery). At these time points, complete blood count, prothrombin time (PT), activated partial thromboplastin

time (aPTT), international normalized ratio (INR), aspartate aminotransferase (SGOT), alanine aminotransferase (SGPT), gGT, alkaline phosphatase, total serum proteins, albumin and bilirubin (direct/indirect) were measured. At baseline and 96 h postoperatively, alpha-glutathione-S-transferase (αGST) and IgG4 antibodies against CYP2E1 were measured. A time period of 4 d was selected because the latency period between the exposure and the clinical evidence of liver damage is variable in the current literature on halothane; its approximate value is estimated to be at least 6 d after first exposure and 3 d after multiple exposures[4]. The same applies to the case reports on desflurane-induced hepatotoxicity, in which the period between exposure and clinical presentation varied between 2-17 d[11,15-20]. Therefore, it was assumed that a time period of 4 d would be appropriate to detect early biochemical changes.

Serum was centrifuged at 1000 rounds/min for 10 min and immediately stored at -80 ℃ until the time of measurements. Complete blood count, coagulation status, SGOT, SGPT, gGT, ALP, serum proteins, and bilirubin were measured directly after sampling, according to the standard perioperative protocol.

Anesthesia in all patients was induced using propofol (2-2.5 mg/kg), fentanyl (3 μg/kg) and cis-atracurium (0.2 mg/kg). Maintenance of anesthesia was achieved with desflurane 6% (in an oxygen/air mixture of 50%) to achieve bispectral index values of 40-50, in addition to a remifentanil infusion as required. Intraoperative monitoring of all patients included systemic blood pressure measurement (invasive when needed), continuous ECG, pulse oxymetry, $ETCO_2$ measurement and bispectral index. Postoperative analgesia included intravenous patient-controlled analgesia with morphine (bolus 1 mg, lockout 10 min) and acetaminophen (1 gr three times daily). In cases of minor surgery without significant postoperative pain, only an acetaminophen-codeine combination was administered (500 mg/30 mg), three times daily. Patients were closely monitored by the anesthesiology team for the efficacy of postoperative analgesia, hemodynamics, oxygenation, nausea and vomiting, two times a day, until the 4th postoperative day. All side effects and complications that occurred during that period were recorded.

A separate group of 8 patients who underwent orthopedic procedures under regional anesthesia was also studied to calibrate the methodology of CYP2E1 IgG4 and αGST measurements. All patients received combined spinal-epidural anesthesia using ropivacaine 0.75% combined with fentanyl, as required. The same serum sampling methodology was followed for these patients. Postoperative analgesia included only morphine administered epidurally (initial dose immediately after surgery) and subsequent acetaminophen-codeine administration (as for the general anesthesia patients).

Serum analysis for CYP2E1 IgG4 antibodies

The determination of serum CYP2E1 IgG4 antibody levels was performed according to a previously described sandwich enzyme-linked immunosorbent assay[21] with slight modifications. Briefly, Immulon 2HB 96-well microtiter plates (ISC BioExpress) were incubated overnight with 0.5 μg/100 μL human CYP2E1 (human CYP2E1 plus P450 reductase plus cytochrome b5 Supersomes (BD Biosciences, Woburn, MA, United States). After washing, plates were incubated with 100 μL serum for 3 h at room temperature and subsequently with 100 μL of a 1:1000 diluted mouse anti-human IgG4 HRP-conjugated second antibody for 2 h at room temperature. The final product was determined by incubation for 20 min with 100 μL of a 1:1 mixture of Color Reagent A (H_2O_2) and Color Reagent Tetramethylbenzidine (R&D Systems, Minneapolis, United States). The reaction was stopped by the addition of 2 N H_2SO_4, and the optical density was determined at 450 nm.

Serum analysis for αGST

The determination of serum αGST was performed using a commercially available ELISA according to the manufacturer's instructions (Eagle Biosciences, Inc, Boston, United States).

Statistical analysis

The Shapiro-Wilk test was performed to test for normal distribution of continuous variables. The results are given as the mean ± SD or as the median and interquartile range (IQR) according to normality of continuous variables. All qualitative variables are presented as absolute and relative frequencies. Student's *t* test or its non-parametric equivalent, the Mann-Whitney *U* test, was used for comparison of continuous variables. Fisher's exact test was employed for comparison of categorical variables.

Mean differences in the liver function tests being studied before and after the intervention (general anesthesia) were investigated by the application of multivariate linear regression models. A stepwise backward-forward technique was applied for the selection of the dependent variables.

All tests were two-tailed, and statistical significance was established at 5% ($P < 0.05$). Data were analyzed using Stata ™ (Version 10.1 MP, Stata Corporation, College Station, TX, United States).

RESULTS

Characteristics of study population

Of the 40 patients included in the study, one was excluded due to the diagnosis of malignancy. The demographic characteristics of patients, such as their age, height, weight and body mass index, are presented in Table 1. Previous anesthetic exposure (to general anesthesia), type and duration of anesthesia, and total length of hospital stay after the operation, are also presented in Table 1. All patients remained hemodynamically stable throughout the procedure, without periods of sustained hypotension (of more than 20% below baseline values) or hypoxia that might interfere with liver function. No patient in this

Table 1 Characteristics of the study population (n = 39)

Demographic characteristics	Mean ± SD/median (IQR) or frequencies[1]	Range[2]
Age (yr)	42 (29-62)	20-75
Gender (M/F)	22(56%) 17(44%)	-
Height (cm)	172.62 (10.55)	152-192
Weight (Kg)	82.7 (20.55)	35-140
BMI (Kg/m^2)	27.66 (6.14)	12.85-41.91
ASA Ⅰ/Ⅱ/Ⅲ	16 (41%)/22 (56%)/1 (3%)	-
Anesthetic data		
Previous anesthesias (no/yes)	12 (31%)/27 (69%)	-
No of previous anesthesias	1 (0-2)	0-6
Duration of anesthesia (min)	150 (90-180)	30-360
Length of stay (d)	5 (4-7)	2-15
Type of operation (n)	Orthopedic: 35 Fractures: 18 Arthroscopies: 12 Knee/hip arthroplasties: 5 Thyroidectomies (non-malignant): 3 Saphenectomy: 1	

[1]Data are presented as mean ± SD or as median [interquartile range (IQR)] according to normality of continuous variables; [2]Qualitative variables are presented as absolute and relative frequencies.

study developed postoperative hepatotoxicity, and all patients were successfully discharged from the hospital.

Comparison of blood test measurements before and after general anaesthesia

No statistically significant difference was observed in the liver function tests (SGOT, SGPT, γGT, bilirubin, INR), αGST or CYP2E1 IgG4 before and after exposure to desflurane. A significant decrease was only observed in the hematocrit, hemoglobin and albumin levels, postoperatively. All data are presented in detail in Table 2.

Multivariate linear regression models were applied using the mean differences of IgG4 and αGST adjusted for gender, BMI, duration of anesthesia, number of times anesthesia was administered previously, and length of hospital stay. A stepwise backward-forward technique was applied for the selection of dependent variables. No significant differences were detected in the mean differences of CYP2E1 IgG4 (before and after general anesthesia) or SGOT, SGPT, γGT, bilirubin and INR ($P > 0.05$). However, significant differences were detected between the mean differences of αGST according to gender, length of hospital stay and duration of general anesthesia. Alpha-glutamyl-S-transferase mean differences were statistically elevated in men by 2.15 ng/mL compared to women when adjusted for BMI, duration of anesthesia, number of times anesthesia was administered previously, and the length of hospital stay. An increase in the duration of anesthesia by one minute was associated with a mean increase in the αGST mean difference of 0.0323 ng/mL. These results are presented in Table 3.

Of the 8 patients who received regional anesthesia, one was excluded due to a malignancy that was diagnosed after the operation. Four women and 3 men were studied, of median age 70 years old (range 65-70) and ASA Ⅱ and Ⅲ. Three of them had received general anesthesia in the past [median 1.5 (range 1-2)], and 4 had not. Although the number of patients who received regional anesthesia was too small to serve as a control group, we compared the median differences (before and after anesthesia, general or regional) of the liver enzymes (SGOT, SGPT, ALP, γGT, αGST) and CYP2E1 IgG4, using the Mann-Whitney U test. There were no significant differences observed for any of the variables studied in this analysis.

Table 2 Comparison of blood test measurements before (baseline) and 96 h after exposure to desflurane

	Baseline measurements	Measurements after intervention	P value[1]
Blood count			
HCT (%)	41.2 (37.4-43)	36.75 (31.65-41.7)	0.016
HBG (g/dL)	13.56 (1.944)	12.01 (1.941)	0.002
WBC	7907.94 (2218.9)	8330 (1826.7)	0.446
PLT (x 10^3)	251 (217-284)	241 (205-276)	0.259
Liver function tests			
SGOT (IU/L)	20 (17-25)	21.5 (17-28)	0.489
SGPT (IU/L)	19 (14-39)	19.5 (13-30)	0.987
ALP (IU/L)	64 (46-77)	54 (47-63)	0.222
γGT (IU/L)	22.5 (13-35)	23 (13-30)	0.532
Direct bilirubin (mg/dL)	0.2 (0.13-0.21)	0.185 (0.1-0.2)	0.277
Indirect bilirubin (mg/dL)	0.5 (0.3-0.7)	0.4 (0.3-0.6)	0.840
Total bilirubin (mg/dL)	0.6 (0.5-1)	0.6 (0.4-0.7)	0.610
Proteins (g/dL)	6.3 (6-6.7)	5.9 (5.35-6.45)	0.082
Albumin (g/dL)	4.1 (3.7-4.3)	3.5 (3.15-3.95)	0.013
PT (s)	11.9 (11.23-13)	12.55 (11.6-13.5)	0.219
aPTT (s)	27.97 (3.09)	29.83 (5.09)	0.125
INR	0.97 (0.92-1.08)	1.02 (0.9-1.1)	0.346
IgG4 (g/L)	0.04 (0.02 -0.5)	0.065 (0.02-0.415)	0.576
αGST (ng/mL)	3.5 (1.69-4.38)	3.03 (1.11-4.87)	0.489

[1]Statistical tests applied: Student's t test, Mann-Whitney U test. Data are presented as the mean ± SD or as the median [interquartile range (IQR)] according to normality of continuous variables. SGOT: Aspartate aminotransferase; SGPT: Alanine aminotransferase; ALP: Alkaline phosphatase; GT: Glutamyl-transpeptidase; PT: Prothrombin time; aPTT: Activated partial thromboplastin time; INR: International normalized ratio; αGST: Alpha-glutathione-S-transferase.

Table 3 Multivariate linear regression model of the mean difference of alpha-glutathione-S-transferase adjusted for gender, body mass index, duration of anesthesia, number of times anesthesia was administered previously, and length of stay

αGST	Coefficient	Standard error	P value	95%CI
Gender	2.15	1.02	0.049[1]	0.0111-4.284
Length of stay	-0.445	0.202	0.04[1]	-0.868-(-0.0229)
Duration	0.0323	0.008	0.001[1]	0.0157-0.0489

[1]Statistical tests applied: Student's t test, Mann-Whitney U test. Data are presented as the mean ± SD or as the median (IQR) according to normality of continuous variables. αGST: Alpha-glutathione-S-transferase.

Previous anesthetic exposure

Twelve of the patients studied had not received general

Table 4 Comparisons of IgG4 and alpha-glutathione-S-transferase levels according to medical history of receiving or not receiving anesthesia previously

	No previous anesthesia (n = 12)	Previous anesthesia (n = 27)	P value[1]
IgG4 levels			
Baseline	0.025 (0-0.04)	0.08 (0.02-0.66)	0.099
96 h after anesthesia	0.035 (0-0.07)	0.105 (0.03-0.74)	0.051
αGST levels			
Baseline	2.94 (1.69-3.94)	3.54 (1.42-5.87)	0.505
96 h after anesthesia	3.825 (3.02-5.4)	2.65 (1.05-4.33)	0.147

[1]Mann-Whitney *U* test. Data are presented as the median interquartile range; αGST: Alpha-glutathione-S-transferase.

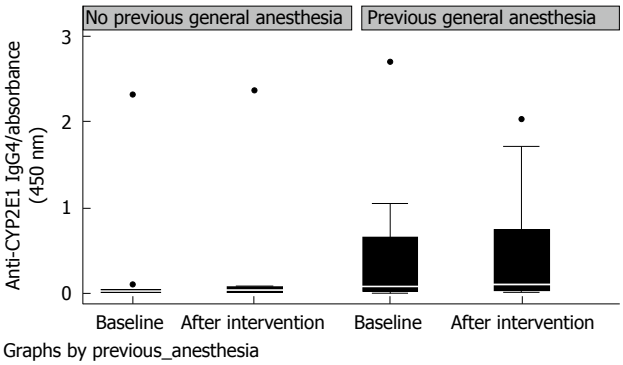

Figure 1 Box plot of anti-CYP2E1 IgG4 values at baseline and 96 h after general anesthesia according to medical history of having received or not received general anesthesia previously.

anesthesia previously. In this subgroup analysis, mean values for CYP2E1 IgG4 levels, at baseline and after desflurane exposure, were 0.025 (0-0.04) and 0.035 (0-0.07), respectively (P = 0.73). Twenty-seven patients had received general anesthesia previously; of these patients, 19 had surgery in childhood. Their CYP2E1 IgG4 levels before and after desflurane exposure were 0.08 (0.02-0.66) and 0.105 (0.03-0.74), respectively (P = 0.59). The changes in IgG4 levels after a new exposure to desflurane for patients who had and had not previously received general anesthesia were not significantly different (P = 0.79). However, CYP2E1 IgG4 levels in patients who had a medical history of previously receiving general anesthesia compared to those who had not, showed borderline statistical significance 96 h after anaesthesia (with P = 0.099 at baseline and P = 0.051 96 h post anesthesia) (Table 4, Figure 1). Alpha-GST baseline levels and levels after the intervention did not differ significantly between patients who had previously received general anesthesia and those who had not (P > 0.1) (Table 4).

DISCUSSION

Severe postoperative liver injury has been reported as a rare complication after anesthesia with halogenated anesthetics[1-4,14-21,23]. The main mechanism responsible is believed to be the production of trifluoroacetylated proteins through the metabolism of halogenated anesthetics from CYP2E1, which act as neoantigens and induce the production of autoantibodies against liver tissue[14,21]. Although newer volatile anesthetics, desflurane especially, are reported to be safe due to their low metabolism by CYP2E1[14], there are several case reports implicating desflurane as the causative agent of IDDIH[11,15-20]. In some cases, it was assumed that the mechanism might be prior sensitization of patients from previous exposures to halothane or other halogenated volatile anesthetics[16].

Njoku *et al*[14] showed that patients with IDDIH had significantly increased CYP2E1 IgG4 autoantibodies compared to control subjects who had never been exposed to halogenated agents. Similarly, in another study, it was observed that the levels of CYP2E1 autoantibodies were asymptomatically increased in pediatric anesthesiologists compared to general anesthesiologists, due to an increased environmental exposure to volatiles[24]. In another study by the same researchers[21] a comparison was made between the levels of CYP2E1 IgG4 in four separate groups: patients with anesthetic-induced IDDIH, pediatric anesthesiologists, general anesthesiologists and healthy controls; CYP2E1 IgG4 levels were significantly higher in patients who developed IDDIH than in all of the other groups. However, no comparison with our results can be made, because there was no direct quantification of the CYP2E1 IgG subclasses. In case reports of desflurane hepatotoxicity, hepatotoxicity occurred between the 2nd and 17th postoperative day and was related to at least one prior administration of anesthesia[11,15-20]. The problem is that CYP2E1 IgG4 levels were quantified and reported to be elevated in only two of these cases[18,20].

In the present study, no patient developed clinical or biochemical indications of liver injury, and there was no statistically significant increase in CYP2E1 IgG4 96 h after receiving anesthesia with desflurane. The hypothesis that previous exposure to halogenated anesthetics may sensitize patients to desflurane, leading them to develop IDDIH after subsequent desflurane exposure, has been stated by various researchers[14]. A cross-sensitization theory between inhalational anesthetics, in addition to the possibility of "immunological memory" of patients who were sensitized to an antigen, may be possible mechanisms to explain this effect[14]. To investigate this possibility, we also performed a subgroup analysis of patients, according to their previous exposure to halogenated anesthetics. Patients who had previously received general anesthesia were studied for their baseline values of CYP2E1 IgG4 and for their tendency to increase these levels after a new exposure to desflurane. The findings did not demonstrate any differences in the degree of increase of CYP2E1 IgG4 between naïve patients and those who had previously received any type of general anesthesia.

Regarding αGST, a multivariate regression model analysis showed that an increase in the duration of anesthesia by one minute was associated with a mean increase in αGST mean difference of 0.0323 ng/mL. This finding may be related to hepatic blood flow alterations and low-grade centrilobular hypoperfusion associated with

the longer duration of anesthesia[25-27]. This possibility is in accordance with the findings of another study of patients undergoing partial hepatectomy under anesthesia with desflurane versus propofol, where it was found that αGST levels 120 min after hepatic vascular declamping were significantly higher in desflurane patients[25]. Further research is required on this subject to investigate alterations of αGST with respect to liver blood flow and duration of anesthesia.

Limitations of this study include the small sample size of patients and the absence of detailed data regarding previous anesthetic exposure. Although the number of patients who previously received general anesthesia is known, the exact agents used (inhalational or intravenous) are unknown. However, most of the patients received anesthesia in childhood, where the use of inhalational agents is a common practice. Additionally, the lack of a longer period of measurement after anesthesia and the absence of more frequent measurements (*i.e.*, more time points) for CYP2E1 IgG4 and αGST are also limitations because there are cases of patients developing alterations after a longer time.

Our results suggest that there was no statistically significant difference between the levels of CYP2E1 IgG4 autoantibodies before and after anesthesia with desflurane. There was no evidence that the levels of αGST or any of the other biochemical markers of liver function were altered after anesthesia with desflurane and no signs that previous anesthetic exposure might affect these levels.

In conclusion, our findings suggest there are no significant differences between the levels of CYP2E1 IgG4 antibodies and αGST before and 96 h after anesthesia with desflurane and no difference between patients with previous anesthetic exposure versus naïve patients. Further research is required to investigate the actual role of CYP2E1 IgG4 in the pathogenesis of halogenated anesthetic-induced liver injury, especially in patients with multiple anesthetic exposures.

ACKNOWLEDGMENTS

Batistaki Chrysanthi and Michalopoulos George contributed equally in study design and conduct and in manuscript preparation. The authors would also like to acknowledge Mrs Agathi Karakosta, MD, MSC in Biostatistics, for statistical analysis of data.

COMMENTS

Background

Volatile anesthetics, mostly halothane, have been implicated as causative agents of Drug Induced Liver Injury (DILI). The most important mechanism for DILI is believed to be a hypersensitivity reaction, which is due to the production of trifluoroacetylated hepatic proteins during metabolism of halothane by the cytochrome P450 2E1 (CYP2E1). With the development of newer volatile anesthetics, the risk of developing DILI has been decreased, due to the minor metabolism of newer agents by the CYP450 2E1 (20%-30% for halothane, in comparison to 0.02% for desflurane). Despite the fact that desflurane seems to have the best safety profile with this regard, and is believed to have minimal, if any, hepatotoxic effect, there have been several case reports published, implicating desflurane as the causative agent of DILI.

Research frontiers

Desflurane is a widely used volatile anesthetic which seems to have the best safety profile regarding liver injury. Despite that, there have been some cases of DILI after desflurane anesthesia and in all of them there was a history of at least one previous general anesthesia. It is very important to identify persons at risk of developing DILI in order to avoid this serious complication. IgG4 CYP2E1 autoantibodies have been implicated in the development of DILI although their specific role is not clear. The measurement of IgG4 CYP2E1 autoantibodies before and after anesthesia with desflurane in patients with and without previous exposure to volatile anesthetics could give some useful information.

Innovations and breakthroughs

In the present study, no patient developed clinical or biochemical indications of liver injury and it was demonstrated that there was no statistically significant increase of CYP2E1 IgG4, 96 h after receiving anesthesia with desflurane. Patients who had previously received general anesthesia were studied as for their baseline values of CYP2E1 IgG4, as well as for their tendency to increase these levels after a new exposure to desflurane. Findings did not demonstrate any significant differences in the degree of increase of CYP2E1 IgG4 between naïve patients and those who had previously received any kind of general anesthesia.

Applications

The study results suggest that desflurane anesthesia is not associated with an increase of IgG4 CYP2E1 autoantibodies and that their role has to be further investigated.

Peer review

Dr. Batistaki C and her colleagues investigated the levels of CYP2E1 IgG4 autoantibody levels and conventional biochemical variables in adult patients before and after anesthesia with desflurane, and found that there was no significant difference in hepatic biochemical variables and CYP2E1 IgG4 levels in patients who received general anesthesia with desflurane. This was an interesting study and the findings also provided them some useful reference in real clinical practice.

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P- Reviewers: Cassard-Doulcier AM, Chen EQ **S- Editor**: Qi Y
L- Editor: A **E- Editor**: Wang CH

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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4254/wjh.v6.i5.347

World J Hepatol 2014 May 27; 6(5): 347-357
ISSN 1948-5182 (online)

SYSTEMATIC REVIEW

Central hepatectomy for centrally located malignant liver tumors: A systematic review

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Received: December 4, 2013 Revised: February 23, 2014
Accepted: May 8, 2014
Published online: May 27, 2014

Abstract

AIM: To study whether central hepatectomy (CH) can achieve similar overall patient survival and disease-free survival rates as conventional major hepatectomies or not.

METHODS: A systematic literature search was performed in MEDLINE for articles published from January 1983 to June 2013 to evaluate the evidence for and against CH in the management of central hepatic malignancies and to compare the perioperative variables and outcomes of CH to lobar/extended hemihepatectomy.

RESULTS: A total of 895 patients were included from 21 relevant studies. Most of these patients who underwent CH were a sub-cohort of larger liver resection studies. Only 4 studies directly compared Central *vs* hemi-/extended hepatectomies. The range of operative time for CH was reported to be 115 to 627 min and Pringle's maneuver was used for vascular control in the majority of studies. The mean intraoperative blood loss during CH ranged from 380 to 2450 mL. The reported morbidity rates ranged from 5.1% to 61.1%, the most common surgical complication was bile leakage and the most common cause of mortality was liver failure. Mortality ranged from 0.0% to 7.1% with an overall mortality of 2.3% following CH. The 1-year overall survival (OS) for patients underwent CH for hepatocellular carcinoma ranged from 67% to 94%; with the 3-year and 5-year OS having a reported range of 44% to 66.8%, and 31.7% to 66.8% respectively.

CONCLUSION: Based on current literature, CH is a promising option for anatomical parenchymal-preserving procedure in patients with centrally located liver malignancies; it appears to be safe and comparable in both perioperative, early and long term outcomes when compared to patients undergoing hemi-/extended hepatectomy. More prospective studies are awaited to further define its role.

Key words: Central hepatectomy; Segment orientated liver resection; Mesohepatectomy; Middle hepatic lobectomy; Central bisegmentectomy

Core tip: Central hepatectomy, defined as anatomical segment 4, 5, 8 ± 1 liver resection, is a promising parenchymal-preserving procedure in patients with centrally located liver malignancies. Based on current evidence, it appears to be safe and comparable in both perioperative, early and long term surgical and oncological outcomes when compared to patients undergoing traditional resections such as hemi-/extended hepatectomy.

Lee SY. Central hepatectomy for centrally located malignant liver tumors: A systematic review. *World J Hepatol* 2014; 6(5): 347-357 Available from: URL: http://www.wjgnet.com/1948-5182/full/v6/i5/347.htm DOI: http://dx.doi.org/10.4254/wjh.v6.i5.347

INTRODUCTION

Surgical resection is the optimal treatment of choice and potential cure for most malignant tumors of the liver if possible[1,2]. With recent improvements in surgical techniques of liver resection, anesthesia and postoperative care, morbidity ranges from 5% to 25% and mortality has improved significantly and has approached zero[3-6]. Centrally located malignancies of the liver such as hepatocellular carcinoma (HCC), Cholangiocarcinoma (CCA) and liver metastases in segments 4, 5, 8 may require extensive resections because of their relationship to major vascular and biliary structures and deep location[7,8]. Traditionally, these centrally located tumors are resected by major resections such as right, left, extended right or extended left hemihepatectomies. Extended or anatomical resections are recommended for oncological reasons; however, these carry a risk of not only significant blood loss, longer operative time but also postoperative liver failure in patients with cirrhosis or poor liver functional reserve or even in patients without cirrhosis[9-11]. Non-anatomical resection is an alternative approach for parenchymal preservation, but it is hindered by intraoperative hemorrhage and betrays oncological principles evident by higher rates of margin positivity and poorer survival outcome[12,13]. With the perpetual lack of donor organs, long waiting time, along with other limitations of liver transplantation, anatomical parenchymal-preserving procedures have an increasing role in treatment of primary and secondary liver malignancies[14].

Central hepatectomy (CH), also known as mesohepatectomy, was first performed for gallbladder cancer in 1972 and is used to describe the operative procedure to resect segments 4, 5, 8 ± 1 (Figure 1)[15-20]. Other synonymous terms used in the literature include central hepatic resection, middle hepatectomy, middle hepatic lobectomy, central bisegmentectomy and central bisectionectomy[20-27]. Regardless of the technical term used, the principle behind this procedure is the same and was not commonly carried out till more recently. In the Brisbane Terminology of Liver Anatomy and Resections by the International Hepatopancreatobiliary Association (IHPBA) in 2000, there was no definition of this surgical procedure[15,16].

The theoretical risks of CH compared to traditional major liver resections such as extended- or hemihepatectomy are obvious. These include a longer operating time, greater intraoperative blood loss, higher risk of biliary and vascular complications, all mainly attributed to the proximity to the hilar structures and the presence of 2 significant resection planes instead of a single plane. Despite this, previous reports showed that CH is safe and achieves comparable complication rates and overall survival rates as conventional major hepatectomies but harbors the advantages of: (1) preserving liver parenchyma with the aim of decreasing the risk of postoperative liver failure; (2) no proven oncological compromises as long as margins are negative and adequate; and (3) increases the opportunity for future repeat resection, if warranted, in cases of recurrent malignancies such as colorectal or neuroendocrine liver metastases[7,8,22,23,25].

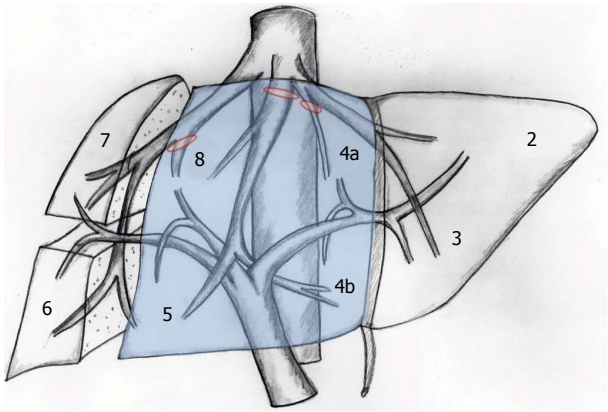

Figure 1 Central hepatectomy-segment orientated resection. Couinaud segments are labeled 2-8; Caudate lobe (Segment 1) is not labelled in this diagram. here) Area shaded blue are the Central segments of 4, 5, 8 which are the segments resected in central hepatectomy (CH). Red rings indicate where the vascular outflow is encountered and ligated during CH.

The current literature directly comparing patients undergoing extended hemi-hepatectomy and CH is lacking[9,15,17,23,25]. There is only one study in the current literature with more than 100 patients (Table 1)[3,7-9,17-20,22,23,25,27-37]. The aim of this review is to analyze and compare the perioperative, early and long- term results of patients with centrally located liver malignancies, between those treated with CH and those treated with hemi-/extended hepatectomy.

MATERIALS AND METHODS

A systematic literature search was performed in MEDLINE (PubMed) from January 1983 to June 2013 to evaluate the evidence supporting CH as a safe procedure for the management of central hepatic tumors and to compare the perioperative, short and long term results of CH to extended/lobar hemihepatectomy. The search used the following medical subgroup headings (MeSH) terms combined with Boolean operators: mesohepatectomy, central hepatectomy, central liver resection, segmentectomy, bisegmentectomy, central trisegmentectomy, bisectionectomy, segmental liver resection and segment oriented liver resection. References of the identified articles were reviewed to identify additional relevant studies. Only full articles published in the English language reporting a series of more than 10 cases were included in the review and effort was made to exclude studies with significant overlap of the same patient cohorts. The literature search was conducted according to PRISMA (preferred reporting items for systematic reviews and meta-analyses) recommendations(Figure 2)[38]. Definitions and nomenclature for liver resections was based on the 2000 IHPBA Brisbane terminology[15,16]. Namely, resection of segments 5 and 8 was named right anterior sectionectomy, while resection of segments 4a and 4b was named left medial sectionectomy. The procedure of segments 4, 5 and 8 resection has now predominantly been termed

Table 1 Characteristics and results of studies on central hepatectomy (1983-2013) *n* (%)

Ref.	Year	*n*	Diagnosis	Operative time (min)	Vascular control	Blood loss (mL)	Morbidity	Mortality	Survival outcome	
Hasegawa *et al*[27]	1989	16	HCC, CRM	300-660	Pedicle occlusion	600-7500	7 (50)	1 (6)	Median OS 34 mo	
Makuuchi *et al*[28]	1993	17	HCC, CCA, CRM	412	NA	1482	7 (41.1)	1 (5.8)	NA	
Nagino *et al*[29]	1998	15	Hilar CCA	NA	NA	NA	NA	NA	NA	
Wu *et al*[17]	1999	15	HCC	474	Pringle's maneuver or pedicle occlusion	2450	3 (20)	0 (0)	1-yr OS 67% 3-yr OS 44% 6-yr OS 30%	1-yr DFS 53% 3-yr DFS 31% 5-yr DFS 21%
Scudamore *et al*[19]	2000	18	HCC, CRM, GBC	238	Pringle's maneuver	914	11 (61.1)	0 (0)	NA	NA
Yamashita *et al*[30]	2001	16	HCC, CCA, metastases, hemangioma, others	NA	NA	NA	NA	NA	NA	NA
[3]Jarnagin *et al*[3]	2002	15	Benign and malignant lesions	NA	NA	NA	NA	NA	NA	NA
Wu *et al*[22]	2002	58	HCC, CCA, metastases	409	Total hepatic flow clamping (28 patients)	1685	8 (8.5)	0 (0)	NA	NA
				399	Selective clamping of ipsilateral blood flow (30 patients)	1159	10 (33.3)	0 (0)	NA	NA
Hu *et al*[23]	2003	52	HCC	265	NA	1030	9 (17)	0 (0)	Median OS 51 mo	Median DFS 23 mo
Chouillard *et al*[25]	2003	19	HCC, metastases, CCA, benign tumor	280	Pringle's maneuver ± hepatic vein clamping	NA	NA	0 (0)	NA	NA
[1]Chen *et al*[18]	2006	118	HCC	128	Pringle's maneuver ± IVC occlusion	592	36 (30.5)	1 (0.8)	NA	NA
Kim *et al*[31]	2006	35	HCC, CCA, hepatic sarcoma	331	Extraglissonian approach and parenchymal Kelly crushing	516	2 (5.7)	1 (2.8)	1-yr OS 94% 2-yr OS 72% 5-yr OS 62%	NA
Giuliante *et al*[32]	2007	18	HCC, metastases	448	Intermittent pedicle clamping	NA	6 (33.3)	0 (0)	NA	NA
[1]Chen *et al*[33]	2007	246	HCC	177 (with preoperative TACE)	Pringle's maneuver ± IVC control	790	31 (34.8)	3 (3.4)	1-yr OS 87.1% 3-yr OS 62.9% 5-yr OS 46.2%	1-yr DFS 75% 3-yr DFS 46.2% 5-yr DFS 31.8%
				115 (without)		420	38 (24.2)	1 (0.6)	1-yr OS 82.2% 3-yr OS 54.4% 5-yr OS 31.7%	1-yr DFS 69.6% 3-yr DFS 38% 5-yr DFS 16.5%
[1]Chen *et al*[7]	2008	256	HCC	174	Pringle's maneuver ± IVC control	750 (Pringle only); 380 (Pringle with IVC control)	72 (28.1)	1 (0.4)	1-yr OS 77.0% 3-yr OS 49.8% 5-yr OS 35.1%	1-yr DFS 59.1% 3-yr DFS 28.8% 5-yr DFS 17.0%
Mehrabi *et al*[34]	2008	48	HCC, metastases, CCA, GBC, hemangioma, other	238	Pringle's maneuver in 9 patients	1120	13 (27.1)	1 (2)	NA	3-yr DFS 47.9%
Lee *et al*[20]	2008	27	HCC	330	Pedicle ligation	1400	12 (44.4)	2 (7.9)	NA	NA

Arkadopoulos *et al*[35]	2012	36	HCC, metastases	180	Selective hepatic vascular exclusion/ Pringle's maneuver (16 patients)	650	6 (37.5)	0 (0)	NA	NA
				150	Sequential hemihepatic vascular control (20 patients)	400	9 (45)	0 (0)	NA	NA
Gallagher *et al*[36]	2013	21	HCC	627	Intermittent Pringle's maneuver	1590	4 (19)	1 (4.8)	1-yr OS 90.5% 3-yr OS 66.8% 5-yr OS 66.8%	1-yr DFS 65% 3-yr DFS 34.8% 5-yr DFS 34.8%
Cheng *et al*[8]	2012	63	HCC	230	Pringle's maneuver	500	8 (12.7)	5 (7.9)	1-yr OS 87.5% 5-yr OS 53.1%	1-yr DFS 50% 5-yr DFS 15%
[3]Yang *et al*[37]	2013	150	HCC	NA	Pringle maneuver	NA	NA	NA	NA	
Total number		895[2]	range	115-627		380-2450	Overall morbidity: 27.5% (range: 12.7%-61.1%)	Overall mortality: 2.3% (range: 0%-7.1 %)		

[1]Indicates multiple studies with overlapping study periods from a single institution; [2]Total number calculated after excluding studies with repeat patients; [3]Limited data available as CH patients were a subset of a larger group of patients undergoing various types of hepatic resections. Overall morbidity and mortality was calculated by considering the number of events as a percentage of the total number of patients in included studies. HCC: Hepatocellular carcinoma; CRM: Colorectal metastases; CCA: Cholangiocarcinoma; GBC: Gallbladder carcinoma; IVC: Inferior vena cava; NA: Not available; OS: Overall survival; DFS: Disease-free survival; TACE: Transarterial chemoembolization; CH: Central hepatectomy.

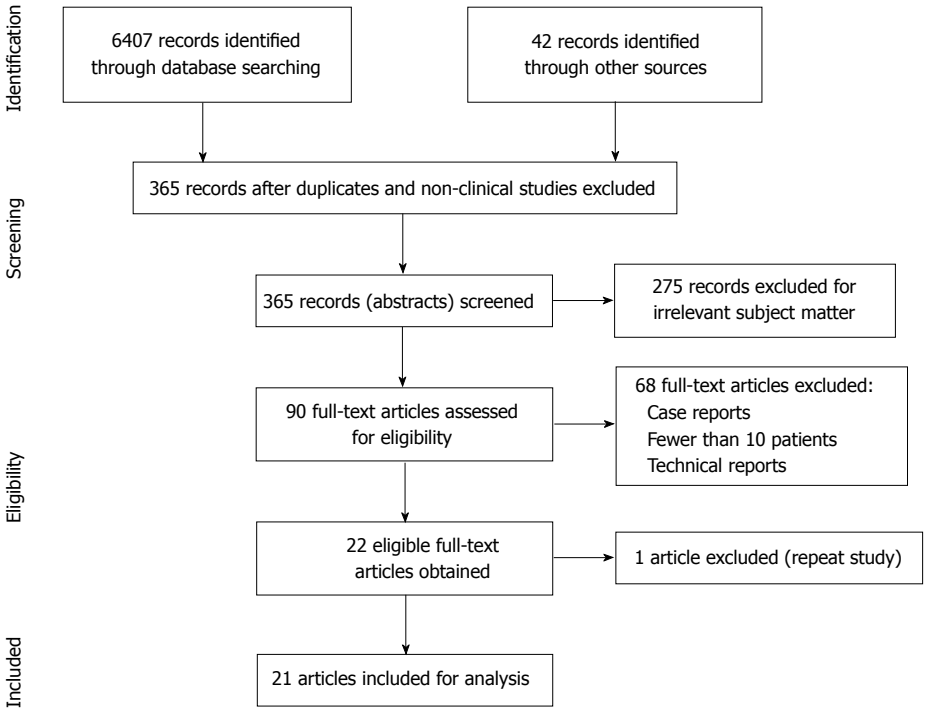

Figure 2 Identification and screening of articles according to preferred reporting items for systematic reviews and meta-analyses recommendations.

central hepatectomy or mesohepatectomy[9,14,17].

When calculating the overall morbidity and mortality, this was calculated as the number of events reported as a percentage of the total number of patients in included studies. In considering individual complications, the number of events or incidences was calculated as a percentage of the total number of complication events in which this data was available. Weighted means were calculated when outcomes were expressed as a mean value.

RESULTS

A literature search on MEDLINE (PubMed) and review of references of relevant articles yielded a total of 90

Table 2 Summary of case-control studies comparing central hepatectomies and lobar/extended hepatectomies *n* (%)

Ref.	Year	Resection type	*n*	Operative time (min)	Blood loss (mL)	Mortality	Morbidity	Complications (*n*)
Wu *et al*[17]	1999	Central hepatectomy	15	474	2450	0 (0)	3 (20)	Bile leak (1), pleural effusion (1), ascites (1)
		Extended hepatectomy	25	348	1863	1 (4)	6 (24)	Bile Leak (2), pleural effusion (1), ascites (1), prolonged jaundice (2), intra-abdominal abscess (2), wound infection (1)
			P value	0.09	0.23	0.43	0.99	-
Scudamore *et al*[19]	2000	Central hepatectomy	18	238	914	0 (0)	1_{intra} (5.5)	Intraoperative bleeding (1), pneumonia (2), intra-abdominal fluid collection (2), fever longer than 48 hours (2), transient fever (2), bile leak (1), late intra-abdominal fluid collection (1)
		Lobar hepatectomy	71	222	1025	1 (1.4)	9_{early} (50) 1_{late} (5.6) 6_{intra} (8.5) 29_{early} (40.8) 3_{late} (4.2)	NA
		Extended hepatectomy	43	304	1628	0 (0)	2_{intra} (4.7) 21_{early} (48.9) 9_{late} (20.9)	NA
			P value	< 0.001	0.009 for extended *vs* central	-	0.05 for late complications	-
Hu *et al*[23]	2003	Central hepatectomy	52	265	NA	0 (0)	9 (17)	Bile leak (3), pleural effusion (3), 1 postoperative massive ascites (1), subphrenic abscess (1)
		Conventional or extended hepatectomy	63	264	NA	2 (3.1)	12 (19)	Bile leak (2), wound infection (4), pneumonia (2), liver failure (2), subphrenic abscess (1), pleural effusion (1)
			P value	0.953		0.408	0.491	-
Cheng *et al*[8]	2012	Central hepatectomy	63	230	500	5 (7.9)	8 (12.7)	Liver failure (2), bile leak (1)[1]
		Hemi-/extended hepatectomies	41	316	750	3 (7.3)	6 (14.6)	Liver failure (2), bile leak (1)
			P value	< 0.001	0.004	1.000	0.777	-
Total		Central hepatectomy	148	Mean 268	Mean 882	3.4% (0%-7.9%)	20.90% (range: 20%-66.7%)	
		Hemi-/extended hepatectomies	243	Mean 299	Mean 1352	2.9% (0%-7.3%)	38.70% (range: 14.6%-74.4%)	

[1]Other complications described included gastrointestinal bleeding, intra-abdominal hematoma, abscess, intra-abdominal bleeding, pneumonia, wound infection, but did not specify the treatment group in which it occurred. Weighted means were calculated for operative time and blood loss. NA: Not available.

articles on central hepatectomy after exclusion of irrelevant articles (Figure 2). Of these, 22 articles were published in English and included more than 10 patients. Of these, one study was excluded from analysis because results of these patients were also reported in a later series by the same author[17,39]. Three articles by Chen *et al*[7,18,33] reported on patients undergoing CH at a single institution with overlapping study periods, with the latest 2008 study of 256 patients constituting the largest reported series of CH at a single institution to date. Of the 21 articles included for analysis, 3 studies were comparative studies between 2 different methods of vascular control during CH, 4 studies compared the results of CH *vs* conventional forms of hepatectomies (hemi- or extended hemihepatectomy), 1 looked at results of CH in patients who had pre-operative transarterial chemoembolization (TACE) as compared to those who did not have preoperative TACE and 1 compared the outcomes of patients who had huge HCC of 10 cm or greater in size, as to compared to that of HCC measuring 5 to 10 cm[19,33,37]. The remaining papers were descriptive and non-comparative studies. The results of these 21 studies, including number of patients, operative time, method of vascular control, operative blood loss, mortality, morbidity and survival data (where available) are summarized in Table 1. The 4 studies which compared the outcomes of CH *vs* conventional hepatectomies are summarized in Table 2.

Table 3 Type and frequency of complications reported following central hepatectomy

Type of complication[1]	Number reported (n = 200)	Frequency (%)
Surgical complications		
Bile leakage/biloma	36	18
Intra-abdominal abscess	16	8
Wound infection	7	3.5
Bleeding	4	2
Intestinal perforation	1	0.5
Medical complications		
Pleural effusion/empyema	62	31
Ascites	29	14.5
Pneumonia/pulmonary infection	13	6.5
Pulmonary edema	6	3
Fever	4	2
Upper gastrointestinal bleeding	3	1.5
Urinary tract infection	3	1.5
Transient hepatic dysfunction/ prolonged jaundice	3	1.5
Hepatic necrosis/liver failure	3	1.5
Acute renal failure	2	1
Stroke	1	0.5
Arrhythmia	1	0.5
Deep vein thrombosis	1	0.5
Other (not specified)	4	2

[1]Calculated out of a total of 200 events.

Study characteristics and operative details

A total of 1259 patients from 21 studies were reported after undergoing CH in the literature. However, after excluding studies with potential repeat patients (due to recruitment with significant overlapping study periods at a single institution), a total of 895 unique patients who had CH were obtained. The indication for central hepatectomy was detailed in 14 studies comprising a total of 659 patients. The main indication for CH was HCC, occurring in 565 patients (85.7%), but was also performed in conditions such as centrally-located liver metastases which accounted for 58 cases (most commonly colorectal in origin). Other diagnoses included CCA/ gallbladder carcinoma (25 cases), hepatic sarcoma (1 case), hemangiomas (2 cases) and occasionally for other benign lesions (4 cases).

The range of operative time for CH was reported to be 115 to 627 min, and Pringle's maneuver was used for vascular control in the majority of studies. The mean intraoperative blood loss during CH ranged from 380 to 2450 mL.

Mortality and morbidity

Data on mortality was available in 16 articles with mortality rates ranging from 0.0% to 7.1%. In nearly half of these studies (7 studies) had zero postoperative mortality following CH. A total of 16 deaths in 17 unique studies comprising 689 patients have been reported, giving an overall mortality of 2.3% following CH. The most common cause of death following CH was liver failure. Concomitant contributing factors that have been reported included sepsis, pneumonia, post-operative bleeding, disseminated intravascular coagulopathy and multi-organ failure. Data on complications following CH were available in 15 studies, with reported morbidity rates ranging from 5.1% to 61.1%. After excluding repeat studies, there were a total of 187 patients reported to have morbidity following CH, out of a total of 680 patients. This gave an overall complication rate of 27.5% (including early and late complications) following CH. A detailed breakdown of the type of complications experienced was available in 13 studies, which accounted for a total of 200 complication events. The most commonly reported surgical complication was bile leakage or biloma formation, which accounted for 18% (36 events) of all complications reported. Bile leakage resolved with conservative treatment in the majority of cases. Other surgical complications reported included wound infection, intra-abdominal abscess, intra-abdominal bleeding/hematoma, and intestinal perforation. Medical complications described following CH included transient hepatic dysfunction/prolonged jaundice/liver failure, ascites, pneumonia/pulmonary infection, pleural effusion/empyema, urinary tract infection, fever, upper gastrointestinal bleeding, renal failure, stroke and deep vein thrombosis (Table 3).

Overall survival

Overall survival (OS) data was available in 8 studies[7,8,17,23,27,31,33,36]. Median survival for HCC treated with CH was reported in 2 studies: this was 34 mo in Hasegawa *et al*[27] (patient diagnosis included both HCC and colorectal liver metastases) and 51 mo in Hu *et al*[23] and Hasegawa *et al*[27] (HCC patients only), Wu *et al*[17] reported a 6-year OS of 30% (HCC, CCA and other liver metastases); Chen *et al*[33] reported a 5-year OS of 31.7% in the group of patients with HCC who did not have preoperative TACE, as compared to the group who had TACE prior to CH with a significantly better 5-year OS of 46.2% (P = 0.043). Overall, the CH group for HCC had 1-year OS ranging from 67% to 94%, with 3-year and 5-year OS having a reported range of 44% to 66.8%, and 31.7% to 66.8% respectively.

Disease-free survival

Seven studies reported disease-free survival[7,8,17,23,33,34,36]. The median Disease-free survival (DFS) in Hu *et al*[23] was 23 mo for HCC. In the remaining HCC studies with DFS data, the range for 1-, 3- and 5-year DFS was 50% to 75%, 28.8% to 46.2% and 15% to 31.8% respectively.

Comparative studies of CH vs hemi-/extended hepatectomies

Of the 21 studies on CH, 4 of these were case-control studies that compared the outcomes following CH *vs* hemi- or extended hepatectomies at their institutions (Table 2)[8,17,19,23]. A total of 148 patients underwent CH and 243 had hemi- or extended hepatectomies performed for their disease in these 4 studies.

Operative time for CH was shown to be not significantly different from that of extended hepatectomies in

the series by Hu *et al*[23] and Wu *et al*[17], while in 2 studies, Scudamore *et al*[19] and Cheng *et al*[8], patients who underwent CH had significantly shorter operative time (238 and 230 min respectively) as compared to extended hepatectomies (304 and 316 min respectively). The overall weighted mean operative time in these 4 studies for CH was 268 min *vs* 299 min for lobar/extended hemihepatectomy. Also, significantly less blood loss was experienced in CH as compared to extended hepatectomies in Cheng *et al*[8] (500 mL in CH *vs* 750 mL for extended hepatectomies, $P = 0.004$) and in Scudamore *et al*[19] (917 mL *vs* 1628 mL, $P = 0.009$). The overall weighted mean intraoperative blood loss in these 4 studies for CH was 882 mL *vs* 1352 mL for lobar/extended hemihepatectomy.

The morbidity rates between CH and hemi-/extended hepatectomy groups were also not significantly different individually in these studies, with the exception of late complications in Scudamore *et al*[19] which was studied as a subgroup. In study by Scudamore *et al*[19], the rate of late complications in extended hepatectomies (20.9%) was found to be higher than that in CH or lobar hepatectomies ($P < 0.05$). The overall morbidity in our review of CH was comparable: 20.9% (range: 20% to 66.7%) for CH *vs* 38.7% (range: 20% to 66.7%) for the hemi-/extended hepatectomy group. There was no statistically significant difference in mortality of patients who underwent CH and hemi/extended hepatectomy groups in any of the 4 studies. Notably, there was zero mortality in 3 out of 4 CH groups, however, there was mortality in the corresponding control groups (hemi-/extended hepatectomy). The overall mortality in the 2 groups were also similar: 3.4% (range: 0.0% to 7.9%) for CH group *vs* 2.9 % (range: 0.0% to 7.3%) for the hemi-/extended hepatectomy group (Table 2).

DISCUSSION

Advances in imaging technology have contributed to the improvements in the understanding of liver anatomy that is based on functional segmental anatomy and forms the foundation for segment-orientated liver surgery[9,12]. Central hepatectomy removes most or the entire left medial sector (segments 4a and 4b) and all or most part of the right anterior sector (segments 5 and 8) with or without segment 1 (Figure 1). It represents an alternative and attractive option for those patients with limited functional liver reserve especially those with liver cirrhosis or those with chemotherapy associated steatohepatitis, because it removes the tumor-bearing segments in entirety while preserving the rest of the liver without necessarily compromising on recurrence or survival outcome[9,40].

In the presence of a large and/or a deep seated tumor located in the central part of the liver (Couinaud segments 4, 5, 8), the resection is more technically challenging due to its proximity to important hilar structures. Central hepatectomy is more surgically daedalean than the conventional anatomical major liver resection because it has 2 resection planes instead of one, the need for preservation of the bilateral peripheral segments and its vasculature and the potential need for 2 bilioenteric anastomoses (*e.g.* for perihilar CCA). It involves the resection of liver territory drained by the middle hepatic vein (HV) along 3 lines of transection planes: the right intersectional plane (to the left of the Right HV), the left intersectional plane (falciform ligament) and the coronal transection plane being above the hilum and anterior to the right posterior sectoral pedicle, the root of the middle HV vein is divided at the bottom of the right and left plane of the parenchymal division; as such, it may require longer vascular occlusion time and alternative pedicle clamping may be required (Figure 1)[22,25]. This is especially pertinent in a cirrhotic liver for parenchymal preservation to minimize the risks of post-operative liver failure. Injury or improper division of these important structures during parenchymal division in CH may result in ischemia or necrosis of the residual peripheral liver leading to liver failure and increased mortality[23].

Preoperative evaluation of hepatic functional reserve includes clinical assessment, liver function test, platelet count, coagulation profile and Child-Pugh classification[14]. The Indocyanine Green (ICG[15]) test has been found to be helpful in predicting the safe limit of liver resection along with Computed tomography volumetric evaluation of the adequate remnant liver volume to minimize post-hepatectomy liver failure[14]. For patients with chronic liver cirrhosis being considered for major resection (≥ 3 segments), pre-operative portal vein embolization (PVE) is a reasonable option to hypertrophy the future liver remnant to minimize risk of post-operative liver failure[14]. Ipsilateral PVE is a feasible preoperative strategy facilitating extended or staged resections, however, with centrally located tumors it is often difficult to determine which side of the portal vein should be embolized; in addition, livers with limited functional reserve will also have lower than expected response to PVE, further limiting its role[41].

Does the preservation of an extra 20% to 25% of liver (40% to 60% parenchymal resection by CH *vs* 60% to 85% resection by extended/lobar hemihepatectomies) justify the increased technical demands of CH? Liver surgery has evolved significantly in past decades. Increased cumulative experience in hepatectomy, improved techniques such as different techniques of vascular occlusion(*e.g.*, Pringle's, total vascular occlusion, sequential vascular occlusion) and the liver hanging maneuver, aided by the advent of advanced surgical technology such as the cavitational ultrasonic surgical aspirator (CUSA, Integra LifeSciences Corporation) and various energy devices (*e.g.*, LigaSure™, Covidien Ltd; Aquamantys®, Medtronic Advanced Energy; Harmonic Scalpel™, Ethicon Endo-Surgery, Inc. Johnson and Johnson Medical Ltd) during liver resection, surgical morbidity and mortality rates have declined markedly as compared with historic data[4,14,23,42-47]. Major vessels and bile ducts in the resection plane can be well visualized, skeletonized, and controlled meticulously during division of the liver parenchyma with these de-

vices (CUSA, LigaSure™, Aquamantys®, Harmonic Scalpel™) as an adjunct to traditional methods such as Kelly clamps, surgical clips and staples. The additional routine use of intraoperative ultrasonography further allows the major vessels and intrahepatic bile ducts to be identified and controlled confidently, as a result, minimizing unexpected major blood loss from vessel injury and avoiding major bile duct injuries[48]. In view of the complexity of CH, sequential or alternative hemihepatic vascular control has been advocated by some authors to minimize clamping time *i.e.*, warm ischemic time of the remnant liver. Arkadopoulos and colleagues demonstrated in a recent study looking at CH comparing 16 patients with selective hepatic vascular exclusion (Pringle's maneuver with hepatic vein outflow occlusion) *vs* 20 patients with sequential hemihepatic vascular control, in which they demonstrated that patients with sequential vascular control received fewer blood transfusions, had less intraoperative blood loss, shorter liver warm ischemic time and lower postoperative transaminitis[35]. Chen *et al*[18] had similar results when they compared 2 cohorts of patients (n = 58 *vs* 60) undergoing CH: they demonstrated that utilizing Pringle's maneuver with IVC occlusion resulted in less blood loss, lower transfusion requirements and less liver damage than Pringle's maneuver alone. In the hands of experienced hepatobiliary surgeons, operative times were also not increased during these procedures, as seen in our review (Table 2: 256 min in CH group *vs* 305 min in the lobar/extended hepatectomy group). Application of a modified Belghiti's liver hanging maneuver (Double liver hanging maneuver) has also been described to help guide the transection planes for CH[44,49]. These newer techniques make central hepatectomy a feasible and safe procedure, especially in experienced hands[9,23,42,50]. More recently, central hepatectomy has also been reported to be performed *via* minimally invasive techniques (laparoscopic or robotic approach)[51-54].

There are 2 main techniques for performing CH. The first involves ligation and division of the central pedicles supplying segment 4, 5 and 8 of the liver segments during liver parenchyma transection under a Pringle's maneuver, while the second involves extrahepatic individual ligation and division of the vessels supplying the segments 4, 5, and 8 prior to parenchyma transection of the liver with or without temporary total hepatic inflow/outflow occlusion[54,55].

Stratopoulos *et al*[9] in 2007 performed a literature review of major series of central hepatectomies. That review encompassed studies published till 2006, and this current review expands on those studies and includes more recent publications on this topic. The surgical mortality rate reported in this earlier review was between 0% and 6.25%. Our review revealed similar mortality rates of 0% to 7.1 % with an overall mortality rate of 2.3%. Consistent with our review, Stratopoulos *et al*[9]'s review reported that the most common cause of perioperative death was liver failure followed by hemorrhage. In our review, the most common surgical complication was bile leak/biloma. Postoperative early morbidity rates were as high as 61% contributed in most part by surgical events such as bile leakage/biliary fistula, hemorrhage/intra-abdominal hematoma, wound infection, intra-abdominal abscess and intestinal perforation as well as medical complications such as liver failure/dysfunction leading to ascites and hepatic encephalopathy, pulmonary infection/pleural effusion/empyema, urinary tract infection, sepsis, upper gastrointestinal bleeding, renal failure, stroke and deep vein thrombosis.

Biliary leakage is one of the most frequently reported intra-abdominal complications after liver resection[30,45,56-58]. The rate of bile leakage in the literature after liver resection has been reported to range from 0% to 11%[23,46,47,59-61]. In hepatectomy without bilioenteric anastomosis, the principal causes of bile leakage are bile oozing from the transected liver surface and intraoperative biliary injury. There are reports that identified central hepatectomy as an independent risk factor for bile leakage because of the presence of two transection planes and exposure of the hepatic hilum[30,56]. In the 4 comparative studies comparing CH *vs* lobar or extended hemihepatectomies, there were no statistically significant differences in bile leak.

In previous reports, CH has been associated with a higher risk of bleeding than conventional major resections[17,32]. Our review revealed that median intraoperative blood loss during CH ranged from 380 to 2450 mL, which is comparable in large liver resection series with major conventional resections[3,4,62].

Most of the patients with reported survival data in this review underwent CH for diagnosis of HCC. The 1-year OS for these patients ranged from 67% to 94%, with 3-year and 5-year OS having a reported range of 44% to 66.8%, and 31.7% to 66.8% respectively. This is comparable to the results from a recent review of survival outcomes looking at 17 studies with more than a total 13000 patients with HCC treated by liver resection, they reported a 1- year survival rate ranging from 67% to 97%, a 3- year survival rate ranging from 34% to 84% and a 5-year survival rate of 17 to 72% was reported[14,63]. A recent study on CH for HCC by Jeng *et al*[40] reported that even with narrow margins (< 5 mm) after CH, there was no negative impact on recurrence and overall survival. Conversely, Nagino *et al*[64] recently commented in a review of over three decades of their experience in the evolution of surgical treatment for perihilar CCA; they reported that limited resections such a CH for perihilar CCA decreased significantly from almost 30% to less than 3% over almost 4 decades with a corresponding improved survival due to more R_0 resections from extended resections. The role of CH for central HCC and perihilar CCA remains to be defined.

Because of the breadth of the current review and the limited available literature of CH as a procedure, the types of studies and the highly descriptive nature of much of the data reviewed, no assessment of the grade quality of individual studies or presence of bias and con-

founders were performed in this review. These studies have inherent selection biases and there is a degree of publication bias as well that is not avoidable due to the retrospective nature of these studies. In addition, because of the lack of high-level evidence and prospective or randomized studies, no objective grading was performed for any specific intervention. The oncological outcomes of HCC in these studies of CH are generalized and not conclusive when compared to HCC undergoing conventional resections due to the lack of detailed clinical and pathological data and risk factors in these studies that determines prognosis and provide strong valid comparison. The literature search was limited to English-language studies within the defined search period and included more recent papers in the past decade that remain highly relevant today. The review nonetheless serves as an updated collection and summary of the cumulative experiences in this relatively novel procedure and approach to segment-orientated liver resection.

Further high-quality and prospective studies with large sample sizes or randomized controlled trials to ascertain the utility and feasibility of central hepatectomy would be important in defining its role in the treatment of centrally-located liver tumors.

In conclusion, this review shows that central hepatectomy can achieve similar overall patient survival and disease-free survival rates as conventional major hepatectomies. Our findings suggest that central hepatectomy may be considered an acceptable procedure for treatment of centrally located malignances and may be the procedure of choice in patients with compromised liver function. It has the advantages of preserving parenchyma and seemingly without oncological compromise however, validation of CH as an oncologically safe procedure requires further prospective studies.

COMMENTS

Background

Central hepatectomy (CH) has similar perioperative outcomes with lobar and extended liver resections and achieves similar overall patient survival and disease-free survival rates as conventional major hepatectomies. Current evidence suggests that CH may be considered an acceptable procedure for treatment of centrally located malignances and may be the procedure of choice in patients with compromised liver function.

Research frontiers

More prospective studies including randomized controlled trials need to be conducted to validate the procedure as an oncologically equivalent and safe operation, specific to different cancer such as hepatocellular carcinoma and colorectal liver metastases, when compared to standard, traditional hepatectomy

Innovations and breakthroughs

Improved surgical and anesthesia experience and better technology has improved the morbidity and mortality of major liver resection and paved the way for safe parenchymal preserving surgery especially in patients with limited liver reserve.

Applications

CH may be applicable in selected patients with central tumors where parenchymal preserving surgery is indicated or preferred.

Terminology

CH also known as mesohepatectomy or central liver resection is used to describe the operative procedure for anatomical liver resection of segments 4, 5, 8 ± 1.

Peer review

In the present manuscript the authors performed a meta-analysis to evaluate the implication of CH for the management of central hepatic malignancies and to compare the perioperative, short and long term results of CH to lobar/extended hemihepatectomy. The authors concluded that CH is a promising option for anatomical parenchymal preserving procedure in patients with centrally located liver malignancies; it is safe and comparable in both perioperative, early and long term outcomes when compared to patients undergoing hemi-/extended hepatectomy.

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P- Reviewers: Chau GY, Cucchetti A, Li LQ, Riehle KJ
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DOI: 10.4254/wjh.v6.i5.358

World J Hepatol 2014 May 27; 6(5): 358-362
ISSN 1948-5182 (online)

CASE REPORT

Ductal paucity and Warkany syndrome in a patient with congenital extrahepatic portocaval shunt

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Received: November 14, 2013 Revised: January 9, 2014
Accepted: March 17, 2014
Published online: May 27, 2014

Abstract

An eleven-year-old clinically dysmorphic and developmentally retarded male child presenting with complaints of 5 episodes of recurrent cholestatic jaundice since 3 years of age was evaluated. Imaging revealed features consistent with congenital extrahepatic portocaval shunt (Abernethy type 1b), multiple regenerative liver nodules and intrahepatic biliary radical dilatation. The presence of ductal paucity and trisomy 8 were confirmed on liver biopsy and karyotyping. The explanation for unusual and previously unreported features in the present case has been proposed.

Key words: Congenital extrahepatic portocaval shunt; Ductal paucity; Warkany syndrome; Trisomy 8

Core tip: This study highlights the association between the congenital extrahepatic portocaval shunt with hepatic ductal paucity and trisomy 8 for the first time in the world literature. Although the exact pathophysiology remains uncertain, plausible explanations are proposed.

Sood V, Khanna R, Alam S, Rawat D, Bhatnagar S, Rastogi A. Ductal paucity and Warkany syndrome in a patient with congenital extrahepatic portocaval shunt. *World J Hepatol* 2014; 6(5): 358-362 Available from: URL: http://www.wjgnet.com/1948-5182/full/v6/i5/358.htm DOI: http://dx.doi.org/10.4254/wjh.v6.i5.358

INTRODUCTION

An eleven-year-old male child was admitted with recurrent episodes of cholestatic jaundice since age three. Each episode was associated with fever, pruritus and clay colored stool, lasting for 10-15 d. There was no history of variceal bleeding, respiratory difficulty, altered sensorium, abdominal distension, oliguria, loose stool, blood in stool, rash, joint pains or any other autoimmune phenomena.

CASE REPORT

The patient was born preterm at 8.5 mo gestation and had indirect hyperbilirubinemia without kernicterus, and was managed with phototherapy. The antenatal period was uneventful. Developmentally, his motor development coincided with his chronological age, but mental age lagged by 5 years.

On examination, his vital parameters were stable. Anthropometry revealed severe malnutrition. There was no pallor, icterus, clubbing, cyanosis, edema, or any peripheral symptoms of chronic liver disease. Dysmorphic features were present and included triangular facies, deep set eyes, antimongoloid slant, bulbous upturned nose tip, mal-aligned upper teeth, retrognathia, camptodactyly, single crease on little finger, multiple finger webs and

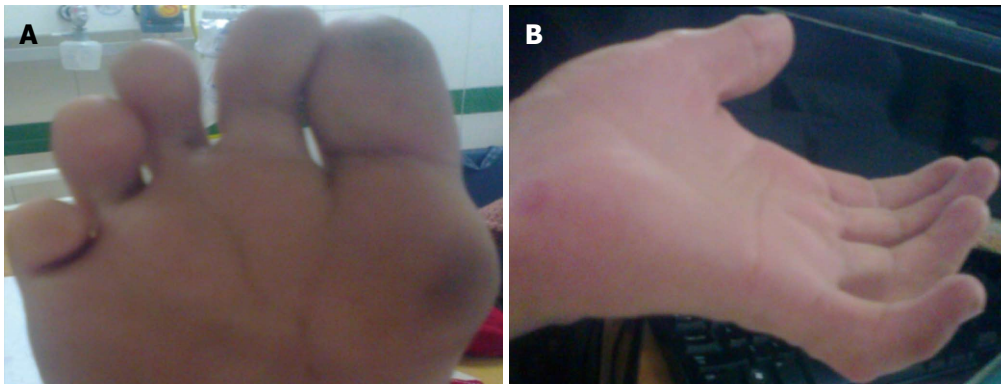

Figure 1 Photograph showing deep plantar furrows (A) and finger webs with camptodactyly (B).

Table 1 Laboratory parameters of the child at various time periods

Parameter	Age			
	6 yr	10 yr	11 yr First contact	11.25 yr Follow-up (episode of cholangitis)
Hb (g/dL)	-	10.7	11	13.6
TLC (cells/mm^3)	-	11300	11600	22200
Platelets (cells 1000/mm^3)	-	329	253	213
Bilirubin (T/D) (mg/dL)	0.8/0.5	1.1/0.5	1.5/0.6	3.18/1.92
AST (IU/L)	100	71	60	242
ALT (IU/L)	104	43	71	148
SAP (IU/L)	410	513	550	604
GGT (IU/L)	-	-	165	224
Albumin (g/dL)	3.7	3.5	3.7	3.3
INR	-	-	1.3	1.1
Ammonia (μg/dL)	-	-	155	229
AFP (ng/mL)	-	6.5	-	1.81
Fasting blood sugar (mg/dL)	-	-	42	72
pO_2 (mmHg) on room air	-	-	79.3	80
A-aO_2 gradient (mmHg)	-	-	26.4	21
BMI Z-score	-	-	-3.5	-3.07
Height Z-score	-	-	-1.7	-1.9

A-aO_2: Alveolar to arterial oxygen gradient; AFP: Alpha-fetoprotein; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; GGTP: Gamma glutamyl transpeptidase; Hb: Hemoglobin; INR: International normalized ratio; pO_2: Partial pressure of oxygen; SAP: Serum alkaline phosphatase; T/D: Total/direct; TLC: Total leukocyte count.

deep plantar furrows (Figure 1). Ophthalmological examination revealed clear lens with normal cornea, iris and fundus. Orthopedic assessment revealed pectus carinatum and elbow contractures with restriction of extension movements. The spine was normal. Abdominal examination revealed no organomegaly or free fluid. Neurological examination was normal with preservation of higher mental, motor and sensory functions. Cardiovascular and respiratory systems were normal.

Laboratory parameters revealed conjugated hyperbilirubinemia with elevated liver enzymes. Synthetic function markers (albumin and prothrombin time) and lipid profile were normal. Serology for hepatitis A, B and C viral infection was negative (Table 1). Doppler ultrasonography (USG) of the abdomen revealed coarse liver with anomalous drainage of the extra-hepatic portal vein (PV) into the inferior vena cava (IVC) with non-visualization of intra-hepatic PV radicles. These findings were confirmed on contrast-enhanced computerized tomography (CT) (Figure 2A), magnetic resonance imaging (MRI) and cholangiopancreaticography (MRCP). Imaging also revealed bilateral nephromegaly and dilatation of intrahepatic biliary radicles (IHBRD, left > right), without evidence of stricture, beading, mass or calculi in the biliary tree (Figure 2B). On MRI, numerous nodules were seen in both liver lobes which were hyper-intense on T1 and showed variable signal on T2 (Figure 2C). These imaging features were consistent with congenital extrahepatic portocaval shunt (CEPS or Abernethy type 1b), multiple regenerative liver nodules and IHBRD.

Subsequent evaluation revealed fasting hypoglycemia and hyperammonemia. Arterial blood gas analysis showed high alveolar-arterial gradient with hypoxemia on room air. Echocardiography showed structurally normal heart with severe shunting on injection of saline contrast, thus suggesting moderate hepatopulmonary syndrome (HPS). Alpha-fetoprotein concentration was normal. Esophagogastroduodenoscopy revealed no varices. A skeletal

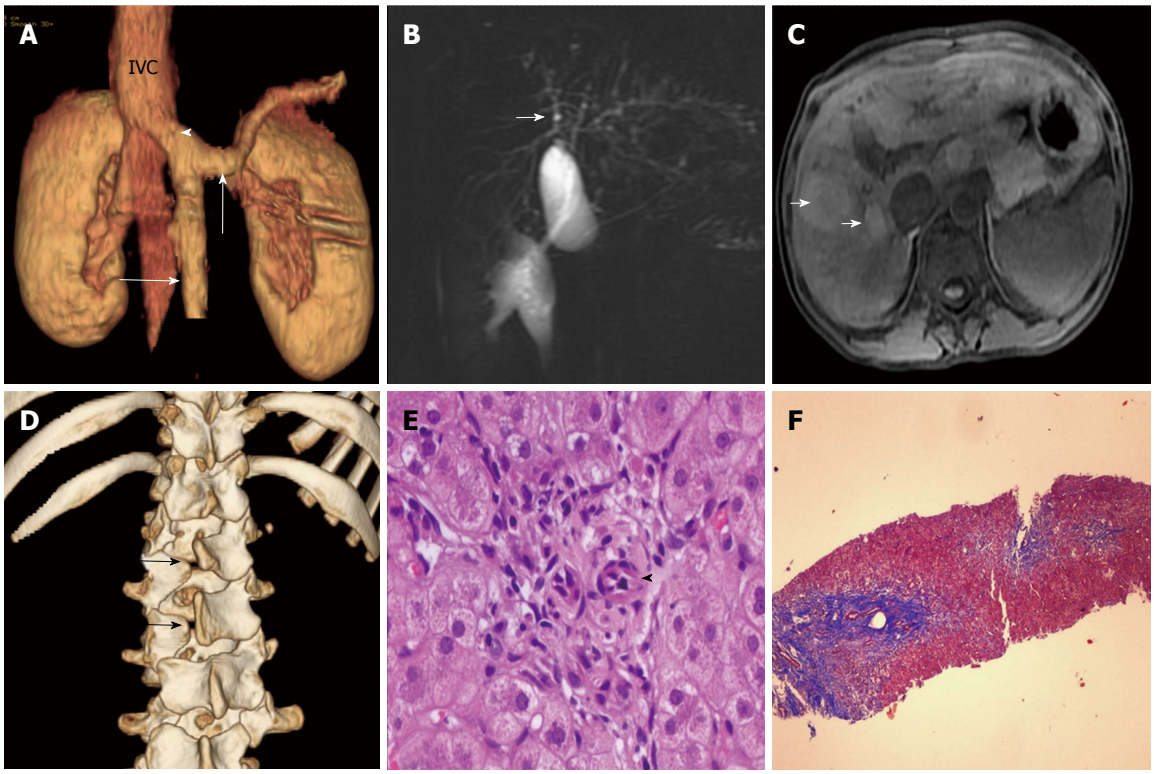

Figure 2 Congenital extrahepatic portocaval shunt (Abernethy Type 1b), multiple regenerative liver nodules and dilatation of intrahepatic biliary radicles. A: Reconstructed 3-D images of contrast-enhanced computerized tomography (CECT) scan showing congenital extrahepatic portosystemic shunt with drainage of the portal vein (arrowhead) into the inferior vena cava-splenic and superior mesenteric veins are shown by vertical and horizontal arrows, respectively; B: Magnetic resonance cholangiopancreaticography images showing dilatation of bilobar intrahepatic biliary radicles (arrow); C: T1-weighted axial images on MR showing well defined, round, hyper-intense lesions in both liver lobes (arrows); D: Reconstructed 3-D CECT images of lumbar spine showing spina bifida at L1 and L2 levels; E, F: Liver biopsy specimen showing preserved acinar architecture; portal tract showing prominent hepatic arteriole (arrowhead) with absence of portal venule and bile ductules (E, hematoxylin and eosin stain, × 400) with periportal fibrosis (F, Masson-trichrome stain, × 40).

survey revealed spina bifida (Figure 2D). Brain imaging was normal. Karyotyping showed mosaic trisomy of chromosome 8. Liver biopsy revealed maintained acinar architecture with mild cholestasis; portal tracts showed total absence of PV profiles, ductal paucity (bile duct: portal tract ratio of 0.3), conspicuous hepatic arteries and periportal fibrosis (Figure 2E and F).

The child was started on sodium benzoate, uncooked cornstarch diet and pentoxiphylline. His fasting hypoglycemia, hyperammonemia and hypoglycemia got corrected after one month of follow-up. He had another episode of jaundice with fever four months later which was managed conservatively. The patient's family was counselled regarding the prognosis including the possible need for liver transplantation (LTx).

DISCUSSION

Congenital extrahepatic portosystemic shunts (CEPS), or Abernethy malformation, is a rare congenital anomaly characterized by shunting of portal venous blood to the systemic circulation. On the basis of the presence of the PV and its intrahepatic radicles and the type of shunt, these malformations were classified by Morgan and Superina as (1) Type 1 (85%), with complete diversion of portal venous blood into the systemic circulation and total absence of intrahepatic PV branches; this was further subclassified as Type 1a, where splenic (SV) and superior mesenteric veins drain separately into the IVC, and Type 1b, when these veins drain after the formation of a short PV trunk, which drains into the IVC in an end-to-side fashion; and (2) Type 2, with intact PV and the presence of a side-to-side portocaval shunt[1]. A recent review suggested a classification based on anatomical site of origin and termination, type of communication with the systemic vein and number of communications[2]. CEPS are known to be associated with various congenital anomalies, particularly cardiovascular, gastrointestinal, genitourinary, skeletal and neurological, and genetic syndromes (Turner's and Goldenhar's)[3]. Our case was Type 1b CEPS without any other major structural malformations, except dysmorphism and spina bifida. He also had nephromegaly with structurally normal kidneys on imaging.

Clinical manifestations in CEPS occur either due to direct entry of intestinal blood and toxins into the systemic circulation or due to long-standing deprivation of PV blood supply with subsequent effects on liver regeneration and metabolism; some features are secondary to associated congenital abnormalities. As per recent reviews, the median age at presentation is 3.7 years with common modes being hypoxemia secondary to HPS or portopulmonary hypertension (26%-34%),

galactosemia (raised blood and urinary concentrations of galactose without enzyme deficiency) (26%), hepatic encephalopathy (HE) or hyperammonemia (9%-34%), neonatal cholestasis (13%) and incidental detection on imaging (9%-21%). Less common presentations are liver dysfunction, hypoglycemia, hepatocellular carcinoma and gastrointestinal bleeding[2,4]. Our patient developed growth failure, hyperammonemia, hypoglycemia, HPS (low partial pressure of oxygen and high alveolar to arterial oxygen gradient on room air) as well as recurrent jaundice (Table 1).

Focal hepatic lesions are common (35%-50%) in CEPS. As the liver is deprived of hepatotrophic factors such as insulin and glucagon, it undergoes atrophy with concomitant regeneration. Regenerative changes manifest as focal nodular hyperplasia, nodular regenerative hyperplasia, hepatocellular adenoma, and rarely cirrhosis, hepatocellular carcinoma and hepatoblastoma[2-4]. Our case had multiple regenerative nodules on imaging with normal AFP.

The diagnosis is established with USG Doppler and CT/MR angiography. Liver biopsy is needed for classification and subsequent management, as well as to establish the nature of the focal lesions. Liver histology in CEPS usually show absence or hypoplastic PVs, thickened hepatic arteries, minimal or moderate portal fibrosis, proliferation of thin vascular, capillary, or lymphatic structures in portal and periportal regions, and occasionally focal ductular proliferation[2]. Our case showed the absence of PV with prominent hepatic arteries and F2 fibrosis on Metavir staging. In addition, our case had ductal paucity, a finding which has not been previously described in CEPS.

Trisomy 8 or Warkany syndrome is a rare disorder. The majority of cases are mosaic as complete trisomy is usually lethal in fetal life. Deep plantar furrow is pathognomonic. Patients also have corneal clouding, strabismus, low set or abnormally shaped ears, bulbous nose tip, cleft palate, camptodactyly, clinodactyly, deep palmar furrow, anomalies related to the skeletal, cardiovascular and urogenital system, and mild to moderate mental retardation[5,6]. Most of these findings were present in our case, and to the best of our knowledge this is the first report of an association between CEPS and trisomy 8.

The presence of recurrent jaundice with bile ductal paucity and IHBRD were unusual features in our case. Recurrent jaundice in CEPS has been described in the literature, but no explanation has been provided[7]. During embryogenesis, PV plays a crucial role in the formation and remodeling of the ductal plate. Conversely, lack of remodeling is frequently associated with abnormalities in the ramification pattern of PV. Thus, both ductal plate malformation (DPM) and PV abnormalities may be interrelated. DPM is also associated with Caroli's syndrome and thus may also explain IHBRD seen in our case[8]. Another possible explanation is a pressure effect on the biliary system by the prominent dilated hepatic artery leading to recurrent cholangitis and ductal paucity secondary to chronic biliary obstruction. Another genetic defect, Alagille's syndrome, associated with mutations in Jagged1 or NOTCH2 genes, is also associated with ductal paucity and dysmorphic features, but our child didn't have other phenotypic features to suggest the disorder[9].

An algorithm for the management of CEPS has been suggested depending on the type of abnormality, symptoms and the presence of liver tumor[2]. Acceptable therapeutic options include LTx in type 1 and shunt occlusion (radiological or interventional) in type 2 cases. Common indications for LTx include HE or hyperammonemia (38%), pulmonary complications (32%) and tumor (15%)[4]. Authors have also proposed shunt occlusion for type 1 cases, presuming that the miniature hepatopetal vessels may enlarge after the procedure[2]. Our patient had moderate subclinical HPS, hyperammonemia and hypoglycemia along with total absence of PV radicles on liver histology, thus mandating LTx.

We describe a case of CEPS type 1b with trisomy 8 with an unusual presentation manifesting as recurrent jaundice, cholangitis and ductal paucity. We discuss the possible cause of recurrent jaundice and ductal paucity in CEPS.

COMMENTS

Case characteristics

Recurrent episodes of cholestatic jaundice, dysmorphism, developmental delay.

Laboratory diagnosis

Conjugated hyperbilirubinemia with elevated liver enzymes, hypoglycemia, hyperammonemia, and hypoxemia with high alveolar-arterial gradient.

Imaging diagnosis

Congenital extrahepatic portocaval shunt (Abernethy Type 1b), multiple regenerative liver nodules and dilatation of intrahepatic biliary radicles.

Pathological diagnosis

Ductal paucity, conspicuous hepatic arteries and periportal fibrosis.

Treatment

Anti-hyperammonemia measures, uncooked cornstarch diet and pentoxiphylline.

Related reports

This is the first report highlighting the association between congenital malformation of portocaval shunt and trisomy 8. The cause of the unusual and previously unreported features in our case such as recurrent jaundice with bile ductal paucity and IHBRD remains unknown.

Term explanation

Congenital extrahepatic portosystemic shunts (CEPS), or Abernethy malformation is a congenital anomaly characterized by shunting of the portal venous blood to the systemic circulation.

Experiences and lessons

CEPS should be considered in the differential diagnosis of a child presenting with developmental delay and liver dysfunction. A simple bedside Doppler ultrasound by an experienced radiologist can help in the identification of this rare anomaly.

Peer review

Article reports the association between a very rare but known congenital malformation of portocaval shunt with not yet reported hepatic ductal paucity and trisomy 8 and also highlights vascular anomalies as one of the causes of recurrent cholestatic jaundice.

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

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16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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