ISSN 1948-5182 (online)

World Journal of *Hepatology*

World J Hepatol 2017 February 18; 9(5): 227-292

Published by Baishideng Publishing Group Inc

WJH
World Journal of Hepatology

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

Editorial Board

2014-2017

WJH World Journal of Hepatology

Contents

Three issues per month Volume 9 Number 5 February 18, 2017

REVIEW

227 Adverse effects of oral antiviral therapy in chronic hepatitis B

Kayaaslan B, Guner R

242 Role of surgical resection for non-colorectal non-neuroendocrine liver metastases

Takemura N, Saiura A

ORIGINAL ARTICLE

Retrospective Study

252 Efficacy and safety of telaprevir- and simeprevir-based triple therapies for older patients with chronic hepatitis C

Yamagiwa S, Ishikawa T, Waguri N, Sugitani S, Wakabayashi H, Ohkoshi S, Tsukishiro T, Takahashi T, Watanabe T, Terai S

Observational Study

263 Malnutrition negatively impacts the quality of life of patients with cirrhosis: An observational study

Rojas-Loureiro G, Servín-Caamaño A, Pérez-Reyes E, Servín-Abad L, Higuera-de la Tijera F

270 Addition of simvastatin to carvedilol non responders: A new pharmacological therapy for treatment of portal hypertension

Wani ZA, Mohapatra S, Khan AA, Mohapatra A, Yatoo GN

SYSTEMATIC REVIEWS

278 Influence of vitamin D on liver fibrosis in chronic hepatitis C: A systematic review and meta-analysis of the pooled clinical trials data

Dadabhai AS, Saberi B, Lobner K, Shinohara RT, Mullin GE

META-ANALYSIS

288 Is it time to rethink combined liver-kidney transplant in hepatitis C patients with advanced fibrosis?

Shah NJ, Russo MW

ABOUT COVER

Editorial Board Member of *World Journal of Hepatology*, Dr. Kun-Ming Chan, MD, Associate Professor, Head, Surgeon, Department of General Surgery, Division of Liver and Transplantation Surgery, Chang Gung Memorial Hospital at Linkou, Chang Gung University College of Medicine, Taoyuan city 33305, Taiwan

AIM AND SCOPE

World Journal of Hepatology (*World J Hepatol*, *WJH*, online ISSN 1948-5182, DOI: 10.4254), is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJH covers topics concerning liver biology/pathology, cirrhosis and its complications, liver fibrosis, liver failure, portal hypertension, hepatitis B and C and inflammatory disorders, steatohepatitis and metabolic liver disease, hepatocellular carcinoma, biliary tract disease, autoimmune disease, cholestatic and biliary disease, transplantation, genetics, epidemiology, microbiology, molecular and cell biology, nutrition, geriatric and pediatric hepatology, diagnosis and screening, endoscopy, imaging, and advanced technology. Priority publication will be given to articles concerning diagnosis and treatment of hepatology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

We encourage authors to submit their manuscripts to *WJH*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great basic and clinical significance.

INDEXING/ABSTRACTING

World Journal of Hepatology is now indexed in PubMed, PubMed Central, and Scopus.

FLYLEAF

I-IV Editorial Board

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Dan Li*
Proofing Editor-in-Chief: *Lian-Sheng Ma*
Responsible Science Editor: *Fang-Fang Ji*
Proofing Editorial Office Director: *Xiu-Xia Song*

NAME OF JOURNAL
World Journal of Hepatology

ISSN
ISSN 1948-5182 (online)

LAUNCH DATE
October 31, 2009

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

EDITORIAL OFFICE
Xiu-Xia Song, Director
World Journal of Hepatology
Baishideng Publishing Group Inc
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

PUBLICATION DATE
February 18, 2017

INSTRUCTIONS TO AUTHORS
http://www.wjgnet.com/bpg/gerinfo/204

ONLINE SUBMISSION
http://www.wjgnet.com/esps/

World Journal of Hepatology

Submit a Manuscript: http://www.wjgnet.com/esps/

World J Hepatol 2017 February 18; 9(5): 227-241

DOI: 10.4254/wjh.v9.i5.227

ISSN 1948-5182 (online)

REVIEW

Adverse effects of oral antiviral therapy in chronic hepatitis B

Bircan Kayaaslan, Rahmet Guner

Bircan Kayaaslan, Rahmet Guner, Department of Infectious Disease and Clinical Microbiology, Yildirim Beyazit University Faculty of Medicine, Ataturk Education and Research Hospital, 06800 Ankara, Turkey

Author contributions: Both authors contributed equally to this paper with conception and design of the study, literature review and analysis, and drafting, critical revision, editing and approval of the final version.

Conflict-of-interest statement: The authors declare no conflict of interests for this article.

Manuscript source: Invited manuscript

Correspondence to: Bircan Kayaaslan, MD, Department of Infectious Disease and Clinical Microbiology, Yildirim Beyazit University Faculty of Medicine, Ataturk Education and Research Hospital, Bilkent Street no: 1, 06800 Ankara, Turkey. drbican@gmail.com
Telephone: +90-505-8267777

Received: April 28, 2016
Peer-review started: May 2, 2016
First decision: November 18, 2016
Revised: November 29, 2016
Accepted: December 7, 2016
Article in press: December 9, 2016
Published online: February 18, 2017

Abstract

Oral nucleoside/nucleotide analogues (NAs) are currently the backbone of chronic hepatitis B (CHB) infection treatment. They are generally well-tolerated by patients and safe to use. To date, a significant number of patients have been treated with NAs. Safety data has accumulated over the years. The aim of this article is to review and update the adverse effects of oral NAs. NAs can cause class adverse effects (*i.e.*, myopathy, neuropathy, lactic acidosis) and dissimilar adverse effects. All NAs carry a "Black Box" warning because of the potential risk for mitochondrial dysfunction. However, these adverse effects are rarely reported. The majority of cases are associated with lamivudine and telbivudine. Adefovir can lead to dose- and time-dependent nephrotoxicity, even at low doses. Tenofovir has significant renal and bone toxicity in patients with human immunodeficiency virus (HIV) infection. However, bone and renal toxicity in patients with CHB are not as prominent as in HIV infection. Entecavir and lamivudine are not generally associated with renal adverse events. Entecavir has been claimed to increase the risk of lactic acidosis in decompensated liver disease and high Model for End-Stage Liver Disease scores. However, current studies reported that entecavir could be safely used in decompensated cirrhosis. An increase in fetal adverse events has not been reported with lamivudine, telbivudine and tenofovir use in pregnant women, while there is no adequate data regarding entecavir and adefovir. Further long-term experience is required to highlight the adverse effects of NAs, especially in special patient populations, including pregnant women, elderly and patients with renal impairment.

Key words: Nucleoside/nucleotide analogues; Adverse events; Lamivudine; Chronic hepatitis B; Side effects; Safety; Telbivudine; Hepatitis B infection; Adefovir; Entecavir; Adverse effects; Tenofovir; Hepatitis B virus

Core tip: Extrahepatic effects of nucleotide analogues (*i.e.*, myopathy, nephropathy, bone disorders) are more commonly indicated in current reports. Some of these adverse events can be attributed to their effect of causing mitochondrial dysfunction. These adverse events are named as "class effects" and mostly associated

with lamivudine and telbivudine treatment. Adefovir is a well-known nephrotoxic agent. Nephrotoxic and bone density loss effects of tenofovir in patients with chronic hepatitis B (CHB) are not as clear as in those with human immunodeficiency virus infection. Serum creatinine, phosphorus and creatine kinase levels should be monitored. Safety profile is a major issue that should not be ignored in the treatment of CHB.

Kayaaslan B, Guner R. Adverse effects of oral antiviral therapy in chronic hepatitis B. *World J Hepatol* 2017; 9(5): 227-241 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i5/227.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i5.227

INTRODUCTION

Chronic hepatitis B (CHB) infection is one of the major causes of chronic liver diseases and affects an estimated 350 to 400 million people worldwide[1]. Up to 15%-40% of patients with CHB are at risk of developing complications including cirrhosis, hepatic decompensation and hepatocellular carcinoma (HCC)[2]. Prevention of disease progression and disease-related complications is the main goal of treatment in CHB and achieved by suppression of hepatitis B virus (HBV) DNA replication[2]. Because CHB requires long-term treatment in the majority of patients, the safety profiles of drugs become important in addition to their antiviral activities. Two different groups of antiviral agents have been approved for the treatment of CHB: Conventional or pegylated interferons (IFN or Peg-IFN), and oral nucleoside/nucleotide analogues (NAs)[2-4]. IFN/Peg-IFNs have some disadvantages, including severe side effects, aggravation of decompensated cirrhosis and autoimmune diseases. NAs have become currently the backbone of CHB treatment because they have been well tolerated by patients for decades without severe side effects[5]. There are currently five NAs approved for the treatment of CHB and they are classified into two groups: Nucleoside analogues (lamivudine, telbivudine and entecavir) and nucleotide analogues (adefovir dipivoxil and tenofovir dipivoxil fumarate)[6]. To date, a significant number of patients have been treated with NAs. Therefore, experience with the efficacy, resistance and safety profile of NAs has increased over the years. The aim of this article is to provide a review of the adverse effects of oral NAs in light of the current data.

All five NAs have a favorable safety profile[7]. However, undesired extrahepatic adverse events may occur during the treatment of CHB infection. The most common extrahepatic adverse events are renal dysfunction, decreased bone mineral density and some neurological findings. Because hepatitis B infection itself may lead to extrahepatic organ involvement[5], determining the source of extrahepatic manifestations may be difficult sometimes during the treatment of CHB. Extrahepatic adverse events may result from mitochondrial toxic effect of NAs. These adverse effects are generally named as "class effects"[8].

CLASS EFFECTS OF NAs

NAs suppress viral replication by the inhibition of the HBV polymerase enzyme. As NAs structures were similar to natural nucleosides, some of these agents can also inhibit human mitochondrial polymerase-γ and cause mitochondrial toxicity[3,5,9]. Mitochondrial toxicity was first noticed during human immunodeficiency virus (HIV) treatment with antiretroviral therapy. Nucleos(t)ide reverse transcriptase inhibitors (NRTIs) are activated by phosphorylation in the cell, and then inhibit HIV reverse transcriptase. Additionally, these drugs also inhibit a human polymerase-γ enzyme, which is responsible for the production of mitochondrial DNA (mtDNA) content. mtDNA-encoded proteins are present in multiple copies in each mitochondrion and responsible for encoding enzyme subunits of the respiratory chain function. Respiratory chain function is required for numerous metabolic pathways, including oxidative synthesis of ATP and synthesis of DNA. The depletion of mtDNA-encoded proteins results in mitochondrial dysfunction that causes impaired oxidative phosphorylation. The other result of human mitochondrial polymerase-γ inhibition is increased reactive oxygen species that cause cellular damage (Figure 1)[5,8,10]. The close relation between NRTIs and mitochondrial toxicity have been described in many reports[5,8,11]. Because NAs lead to a minimal mitochondrial polymerase-γ inhibition, NAs-associated mitochondrial toxicity cases have been rarely reported. All NAs carry a warning of mitochondrial toxicity as part of their prescribing information[5,8]. The clinical manifestations of mitochondrial toxicity include hematologic disorders, peripheral neuropathy, skeletal and cardiac myopathy, pancreatitis, hepatic failure and lactic acidosis[8,11].

The most remarkable examples of mitochondrial toxicity were reported with clevudine therapy. Clevudine is a thymidine-nucleoside analogue approved in South Korea and the Philippines for the treatment of CHB. Although no mitochondrial dysfunction findings had been detected in preclinical studies, multi-center international phase Ⅲ studies were terminated due to the emergence of clevudine-associated myopathy cases. Clevudine had been shown to be peripherally phosphorylated by mitochondrial thymidine kinase and to accumulate in cells rich in mitochondria[5]. South Korea revoked its approval because of indirect adverse effects[12-14]. The emergence of an association between clevudine and myopathy served as a reminder that all NAs have a potential risk for mitochondrial toxicity. Among the NAs, lamivudine and telbivudine are the agents most frequently reported to be associated with myopathy and peripheral neuropathy (Table 1). Long-peripheral neurons were more susceptible to mitochondrial toxic effect of NAs due to length-dependent effect[15]. Xu *et al*[16] performed muscle and nerve biopsy in the 6 cases

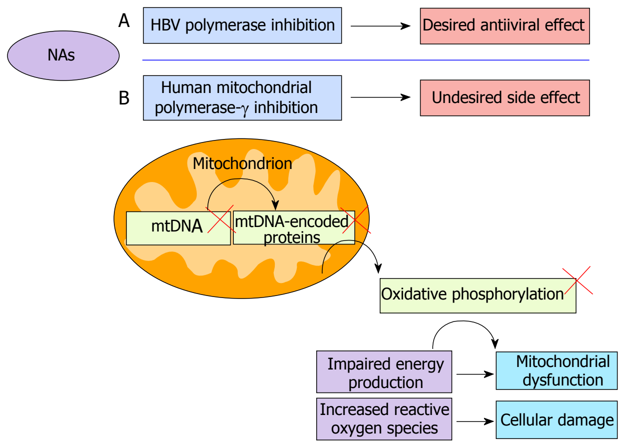

Figure 1 Effects of nucleos(t)ide analogues. A: NAs show antiviral effect by inhibition of hepatitis B virus (HBV) polymerase; B: NAs also inhibits human mitochondrial polymerase-γ enzyme. Thus, mitochondrial DNA (mtDNA) can not be synthesized. Oxidative phosphorylation is impaired. There are two consequences of this: Impaired energy production and increased reactive oxygen species that cause cellular damage. NAs: Nucleos(t)ide analogues.

of NAs-associated myopathy or neuropathy and revealed similar changes in all the muscle and nerve biopsy samples of the patients in light or electronic microscopy and showed the decrease of the mitochondrial DNA by the quantitative real-time PCR in the affected muscle. Although an association between telbivudine and mitochondrial toxicity was not detected *in vitro* studies[12], telbivudine-associated myopathy and creatine kinase (CK) elevations have been reported repeatedly in real-life patients after phase studies. Myopathy may be accompanied by neuropathy in some of patients given telbivudine or lamivudine for the treatment of CHB infection. In one study, 3 of 6 patients with lamivudine or telbivudine-associated myopathy had a complaint of numbness in the distal end of limbs, suggesting peripheral neuropathy. The presence of neuropathy was confirmed by the electrophysiological studies and nerve biopsies by the study team[16]. Neuropathy cases have been reported more commonly in patients who have been treated with a combination therapy of telbivudine and Peg-IFN alfa-2a. Combination therapy provided a rapid reduction in HBV DNA level compared to telbivudine or Peg-IFN alfa-2a monotherapy. However, the risk of peripheral neuropathy has been reported to increase up to 20% in combination with Peg-IFN[10,12,15,17].

Myopathy is characterized by CK elevation alongside muscle pain and weakness. CK elevations are among the well-described adverse effects of NAs, but they are not specific for myopathy and may be associated with strenuous exercise and many other illnesses. CK elevations may occur in patients treated with all approved NAs for CHB. However, the incidence of myopathy is very low during the treatment with adefovir, entecavir and tenofovir, and similar to comparative groups. The causal relationship has not been elucidated as of yet[3,18]. Myopathy cases can be seen in every age group (25-82 years). There is no difference between male and female patients in terms of myopathy incidence. The mean onset time of myopathy from the initiation of NAs was reported as 6.4 mo, but it can occur even if in the 5th year of treatment. Myopathy cases had been mostly reported from the South Korea and China, but the association between myopathy and race remains unclear[19].

LAMIVUDINE

Lamivudine is the first oral NA approved by the United States Food and Drug Administration (FDA) for the treatment of CHB in 1998 at a dose of 100 mg/d. It is an analogue of cytidine [2′,3′-dideoxy-3′thiacytidine (3TC)] and phosphorylated to its active triphosphates form by intracellular deoxycytidine kinase enzyme. The active anabolite prevents HBV replication by competitively inhibiting viral reverse transcriptase and terminating proviral DNA chain extension[20]. Lamivudine has been the most experienced oral antiviral in CHB patients[8,20]. It can be used effectively in a broad range of patients, with minimal adverse effects[21]. However, long-term treatment of lamivudine is associated with high rates of drug resistance, which lead to virological relapse and biochemical flare[1-3,8]. Therefore, lamivudine is recommended as a second-line therapy for the treatment of CHB[1,2].

Long-term lamivudine treatment was generally well-tolerated by CHB patients[21,22]. In the GLOBE trial, a large, multi-center phase Ⅲ study, of the 1367 CHB patients who received telbivudine and lamivudine, adverse events were reported in 23% of the lamivudine recipients, similar to the findings for the telbivudine recipients (29%). The most common adverse events were upper respiratory tract infection (16.2%), naso-pharyngitis (13.1%), headache (13.4%) and fatigue (12.1%). Of the patients, 6% (44) experienced serious adverse events[23]. The primary adverse event was reported as hepatic flares due to emergence of lamivudine-resistant HBV with prolonged treatment. After 4 years, hepatic decompensation and other severe adverse effects in-creased among patients with lamivudine resistance[24]. In an Asian study by Leung *et al*[22], 12% (n = 7) of patients treated with lamivudine experienced severe side effects. Most of these were increased transaminase and CK levels, and resolved spontaneously. Increased alanine aminotransferase (ALT) levels were generally associated with emergence of YMDD mutant strains and had no clinical importance. In another study conducted among 998 patients with hepatitis B e antigen (HBeAg)-positive compensated liver disease who were treated with lamivudine for up to 6 years, lamivudine demonstrated a good safety profile, with only a 5% rate of severe adverse events[24]. Similarly, lamivudine has been found to be effective in HBV DNA decrease, ALT normalization and histological improvement, and it was well-tolerated by patients with cirrhosis. Lamivudine had been used in patients with acute or fulminant hepatitis without any adverse event, and led to fast recovery and increased

Table 1 Characteristics of approved oral antiviral drugs for chronic hepatitis B treatment

NAs (approval year)	Class effect	Renal effect	Most common adverse events	Laboratory monitoring	Rare severe adverse reactions	Pregnancy category	Detection in breastfeeding
Lamivudine (1998)	Myopathy and neuropathy cases were reported	No significant effect	Upper respiratory tract infection, nasopharyngitis, headache and fatigue ALT flairs CK elevation may occur (usually not requiring cessation of drug)	Serum ALT and bilirubin	Rhabdomyolysis, acute dystonia, pancreatitis Rare lactic acidosis	C	Yes
Telbivudine (2006)	Myopathy and neuropathy cases were reported (especially in combination with Peg- IFN)	Nephroprotective effect Increase in GFR	Upper respiratory tract infection, nasopharyngitis, headache and fatigue Increased incidence of CK elevation (usually asymptomatic and self-limiting, not required cessation of drug)	CK level Serum lactate	Lactic acidosis	B	Yes
Adefovir (2002)	Very rare, No increased incidence of myopathy compared to placebo	Clinically significant nephrotoxicity Decrease in GFR	Pharyngitis, asteni, headache, abdominal pain, flu-like symptoms and nausea	Serum creatinine and phosphate level	Hypophosphatemia Fanconi syndrome	C	Unknown, not recommend for use
Entecavir (2005)	Very rare, No increased incidence of mitochondrial toxicity in combination of entecavir with other NAs and IFN	No decrease in GFR	Headache, upper respiratory tract infection, cough, nasopharyngitis, fatigue, dizziness, upper abdominal pain and nausea	Serum lactate	Lactic acidosis	C	Unknown, not recommend for use
Tenofovir (2008)	Very rare, No increased incidence of myopathy compared to placebo	May decrease GFR, clinically insignificant Nephrotoxic in HIV patients Hypophosphatemia	Headache, nasopharyngitis, back pain, nausea Bone mineral density loss (more prominent in HIV patients)	Serum creatinine and phosphate level BMD		B	Yes

NAs: Nucleos(t)ide analogues; ALT: Alanine aminotransferase; CK: Creatine kinase; IFN: Interferon; GFR: Glomerular filtration rate; HIV: Human immunodeficiency virus; BMD: Bone mineral density.

survival[25].

Lamivudine has a good safety profile in different patient populations having some comorbid diseases. It is the most experienced drug for preemptive treatment of hepatitis B infection in solid-organ recipient and immunosuppressive patients[1]. There are limited data for experiences with the other NAs[26]. Although highly potent oral NAs with high genetic barriers to antiviral resistance, such as entecavir and tenofovir, have become the current preferred regimen, lamivudine remains a therapeutic option for hepatitis B prophylaxis since it is the most cost-effective choice for these patients[27,28]. Lamivudine has been well tolerated by patients receiving immunosuppressive treatment. In a systematic review investigating the preventive effect of lamivudine on chemotherapy - induced hepatitis B-related morbidity and mortality in hepatitis B surface antigen (HBsAg)-positive patients with cancer, none of the eight studies that recorded safety profile of lamivudine reported any significant adverse events[29]. Lamivudine has also been used safely in children without any serious side effects. In one study, only slight and transient increase of ALT levels were reported in 6.8% of children with CHB, without any complaint or clinical findings[30].

Serious adverse events have rarely been reported with lamivudine treatment[31,32]. Lamivudine-induced rhabdomyolysis is one of them and characterized by a triad of muscle weakness, myalgia and abnormal laboratory findings including CK elevation, increased urine and blood myoglobin level, and acute renal injury. Tubular damage and obstruction is considered the main reason underlying pathogenesis[31-33]. Clinical and laboratory findings improve generally within a few days after cessation of the drug. However, in one case, rhabdomyolysis relapsed after readministration of lamivudine for HBV infection prophylaxis and resolved completely after discontinuation of the drug again[34]. The mortality rate was reported to be high in patients who developed rhabdomyolysis and may be reduced by the early recognition of the disease and fluid resuscitations[31].

Lamivudine-induced acute dystonic reaction was reported in 2 patients, and the acute dystonia resolved after discontinuing the lamivudine therapy[35]. Lamivudine-associated ichthyosiform eruptions and pancreatitis cases have been reported in the literature[25,36-38].

TELBIVUDINE

Telbivudine is a thymidine nucleoside analogue which selectively inhibits HBV DNA synthesis. It was approved in 2006 for the treatment of CHB patients at a dose of 600 mg/d. Telbivudine is a more potent NA against HBV compared to lamivudine and adefovir[3,39]. However, high resistance rates limit the use of telbivudine as the firstline therapy[2,3]. Upper respiratory tract infection, nasopharyngitis, fatigue and headache were reported as the most frequent adverse events associated with telbivudine use. Adverse events' frequencies were found to be similar in lamivudine and telbivudine groups. However, Grade 3/4 increase in CK level occurred more commonly in patients given telbivudine (12.9% *vs* 4.1%), but these were not associated with musculoskeletal adverse events and no rhabdomyolysis cases were detected during the study period[23]. CK elevations were generally self-limiting and asymptomatic. Discontinuation of telbivudine was not required in most of the cases. Telbivudine-associated myopathy and CK elevations have been reported in several studies[12,40-42]. Zou *et al*[41] conducted a prospective study to investigate clinical features and risk factors of telbivudine-associated myopathy and CK elevations. The serum CK levels of 200 patients treated with telbivudine were analyzed. The 3-year cumulative incidence of CK elevations was considerably high (84.3%). Nine patients (5%) experienced myopathy and were required to discontinue telbivudine therapy in 3 of those. None of the patients developed rhabdomyolysis. CK elevations were reported to occur in males more often than in females and in those with HBeAg negativit and aged < 45 years. In another study in which 105 patients given telbivudine were evaluated for adverse reactions, 5 presented serious adverse events. There was nervous system damage in 3 of the cases and cardiac arrhythmia in 1 case. All 5 patients had elevated CK enzymes. Therefore, it is recommended that CHB patients treated with telbivudine should be monitored closely for musculoskeletal symptoms and CK enzyme levels[3].

Some infrequent but serious side effects were reported in previous studies. Lactic acidosis is one of them and it was reported also in patients treated with all the other nucleos(t)ide analogues[43]. It results from mitochondrial dysfunction or loss due to the inhibitor activity of telbivudine on human mitochondrial DNA polymerase-γ. A few lactic acidosis cases depending on telbivudine therapy were reported in the literature. The symptoms of patients were anorexia, nausea, vomiting, muscle pain and weakness in upper and lower extremities. The laboratory tests revealed elevated serum CK levels and hyperlactatemia[43]. One patient's complaints continued even after the withdrawal of telbivudine treatment, and the patient recovered after venovenous hemodiafiltration. To diagnose hyperlactatemia, the patients should be monitored by periodic (3-6 mo interval) lactate measurements, in addition to the CK monitoring.

The mechanism of adverse events associated with telbivudine use has not yet been defined. Because adverse events may occur in multiple organs including muscles, nervous and cardiac systems, Zhang *et al*[42] suggested that the mechanism is associated with cell energy metabolism. Deficiency in manufacture of the energy molecule ATP and, therefore, inadequate supplementation of substrate for oxidative phosphorylation causes mitochondrial damage. Highly energy-dependent organs such as nerves, heart and muscles are the most susceptible to mitochondrial dysfunction. Telbivudine leads to adverse events in these organs. However, to establish a link between adverse events and mitochondrial disease, muscle biopsy and DNA studies should be done[42].

Synergistic effect can occur in case of simultaneous use of two drugs. A study comparing telbivudine and lamivudine combination and lamivudine monotherapy reported that the addition of telbivudine to lamivudine treatment did not increase the toxic adverse effects[44]. However, the combination of telbivudine with Peg-IFN caused peripheral neuropathy in 17.0% of patients. For this reason, telbivudine should not be recommended in combination with Peg-IFN[8].

ADEFOVIR DIPIVOXIL

Adefovir dipivoxil is an oral prodrug of the nucleotide analogue adefovir, approved for CHB treatment at 10 mg/d dose in 2002. It was used initially in patients with HIV infection, but its use was abandoned due to the fact that higher doses of adefovir led to nephrotoxicity[8]. Adefovir improves histological, biochemical and virological outcomes in CHB patients with lamivudine resistance. The rates of adverse events in patients given adefovir are similar to those given placebo[45-48]. The most common adverse events were pharyngitis, asteni, headache, abdominal pain, flu-like symptoms and nausea[45]. In a randomized controlled study, adverse events were similar in two groups, but headache and abdominal pain occurred more frequently in the adefovir group than in the placebo group. However, these adverse events did not lead to discontinuation of the study drug[48]. Adefovir is associated with dose-dependent renal toxicity. The nephrotoxic effect of adefovir was discussed in the section below on "Renal Safety of NAs".

Myopathy cases were reported in CHB patients given adefovir treatment, but its incidence was similar to patients receiving placebo[12]. Adefovir-related lactic acidosis may occur when combined with other NAs[49]. The development of resistance to adefovir therapy is another undesirable event. Drug resistance was reported in 26% of CHB patients treated with adefovir, after

5 years[8]. The resistance rate of adefovir in patients with lamivudine resistance who were given adefovir add-on lamivudine rescue therapy was 6% at the end of 5 years[50]. To optimize therapy in lamivudine-resistant patients, it is recommended not to discontinue lamivudine therapy for a while after initiating adefovir[8].

ENTECAVIR

Entecavir is a highly selective guanosine nucleoside analogue, approved by the FDA at a dose 0.5 mg in treatment naive and 1 mg/d in lamivudine-resistant CHB patients in 2005[3,51]. It inhibits three steps of viral replication, which involves HBV polymerase priming, reverse transcription of the pre-genomic messenger RNA and synthesis of the positive-stranded HBV DNA[3]. Entecavir is a well-tolerated antiviral agent in CHB patients, with rates of adverse events similar to placebo or lamivudine therapy. In a comparative study, the adverse event rate was found to be similar in patients given entecavir monotherapy to those given combination of entecavir and IFN[52]. Long-term use was reported to be associated with a very low rate of side effects. Adverse events were not dose-related; their frequencies were similar between 0.5 or 1 mg doses of entecavir[51,53]. The most frequent adverse events in clinical trials were headache (17%-23%), upper respiratory tract infection (18%-20%), cough (12%-15%), nasopharyngitis (9%-5%), fatigue (10%-13%), dizziness (9%), upper abdominal pain (9%) and nausea (6%-8%). Most of these adverse effects were mild or moderate severity and did not require discontinuation of the drug[51,54]. Severe adverse events accounted for 7%-10% and discontinuation of therapy accounted for 1%-2% of patients[51]. In a randomized controlled study, severe adverse events occurred in 4.7% of pediatric patients (n = 8), and only one of them discontinued entecavir due to headache. This adverse event was not attributed to the study drug[54]. Although preclinical data reported an association between long-term entecavir use and carcinogenicity, to date, no evidence has been detected regarding occurrence of cancer due to entecavir therapy[55].

The FDA requires all approved NAs to include a "Black Box" warning in their product label regarding potential mitochondrial toxicity[56]. Entecavir is the most innocent antiviral agent leading to mitochondrial toxicity among the effective therapies in CHB treatments. In long-term cell culture studies, entecavir has been observed to have very low potential for mitochondrial toxicity in *in vitro* cultures studies at the highest levels tested, 300 μmol/L. Combination of entecavir with the other NAs also did not cause an increase in the risk of other drugs[8,57]. Entecavir-associated myopathy and peripheral neuropathy cases were very rarely reported in the literature[3,15,19]. Although a study reported similar CK elevation rates with both telbivudine and entecavir therapy, there were not many studies supporting this[58]. In a meta-analysis, six randomized controlled trials involving 555 patients treated with telbivudine and entecavir for 24 or 52 wk were evaluated. Both drugs had similar antiviral and biochemical effects. However, the entecavir group was reported have greater safety than the telbivudine group, in terms of adverse events[59]. In another meta-analysis comparing the effects of telbivudine and entecavir in HBeAg-positive CHB patients, thirteen trials (3925 patients in total) were evaluated. Adverse effects were reported in 10 trials and CK elevations in 5 trials. The rates of increased CK were found to be statistically higher in the telbivudine group than in the entecavir group[60].

Lactic acidosis can also occur during treatment with NAs as a result of mitochondrial toxicity. US prescribing information for entecavir and the other NAs carries a warning regarding the risk of lactic acidosis in CHB patients treated with NAs[61-64]. Entecavir is a good option for the treatment of CHB patients with decompensated cirrhosis because of the rapid effect on HBV decline and low resistance rates. However, it was suggested that a high Model for End-Stage Liver Disease (MELD) score that is used to detect highly impaired liver function can be associated with lactic acidosis in patients receiving entecavir[49]. One retrospective study identified 5 cases of lactic acidosis among 16 entecavir-recipient CHB patients with cirrhosis. One of them died, and the lactic acidosis resolved within 4-5 d after withdrawal of entecavir in the remaining 4 cases. All patients who developed lactic acidosis had a MELD score of at least 20 (22-38), whereas the patients who did not develop lactic acidosis had a MELD score below 18. A significant (P = 0.002) correlation was seen between the MELD score and the development of lactic acidosis[49]. However, a small retrospective study did not find an increased risk of lactic acidosis in the CHB patients with decompensated liver disease and high MELD scores during entecavir treatment, compared to those who have non-HBV-related decompensated liver disease and similar clinical features[65,66]. Entecavir has been reported to have a high safety profile in decompensated patients and recommended as one of the first-line treatment choices of CHB patients with decompensated liver disease in an Asian-Pacific consensus statement[67,68]. Nevertheless, the patients should be monitored cautiously for the risk of lactic acidosis during the treatment and entecavir should be suspended in the case of suspected lactic acidosis[49,66].

Patients with severe acidosis complained of nausea, dyspnea and weakness, and showed a reduced general physical condition, impaired consciousness and tachypnea. In addition, 2 of 3 patients with severe acidosis suffered from paresthesia and the remaining 1 patient developed hepatic steatosis typical for mitochondrial toxicity. ALT flares, potentially leading to decompensated hepatic disease, can be another serious health problem in a patient given entecavir for CHB. In clinical trials, ALT flare had been reported to occur in a small percentage of patients treated with entecavir and to resolve even if the treatment continued. In an open-label study evaluating the safety and tolerability of entecavir, Grade 3 and 4 adverse events were detected in 19% of the patients, with only 4% of them possibly related to entecavir. These Grade 3 and 4 adverse events were myalgia, neuropathy, increased lipase, increased creatinine and lactate, CK elevation, decreased bicarbonate and pancreatitis. Entecavir treatment was discontinued in only 1% of cases due to adverse events. ALT flares were reported in 3% of the patients during the treatment, and were associated with inhibition of viral replication, at least 2 $\log_{10}$ decrease of HBV DNA[68]. In a multicenter European study investigating the incidence and outcome of ALT flares during long-term entecavir in CHB, 729 patients treated with entecavir for a median of 3.5 years were evaluated. Flares were classified as host-induced (preceded by HBV DNA decline), virus-induced (HBV DNA increase) or indeterminate (stable HBV DNA). A total cumulative incidence of ALT flare was 6.3% (30) at year 5. Of them, 12 were host -induced and associated with biochemical remission. HBeAg and HBsAg seroconversion was observed in only these host-induced flares. Virus-induced flares were reported to be associated with entecavir resistance and non-compliance to the therapy[69]. Therefore, long-term use of entecavir is generally safe and associated with low rates of serious adverse events, and discontinuation of the treatment is rarely required. ALT flares were low in patients receiving entecavir and generally associated with the improvement of liver disease. In current guidelines, entecavir is also recommended as treatment and prophylaxis of CHB infection in patients with renal transplant due to being an agent without signs of nephrotoxicity[2].

TENOFOVIR

Tenofovir disoproxil fumarate (TDF) is a prodrug of tenofovir that has been approved as a nucleotide analogue by the United States FDA for use in HIV infection in 2001 and in CHB infection in 2008 at a dose of 300 mg[8]. TDF is converted to tenofovir by hydrolysis and then phosphorylated by cellular enzymes to tenofovir diphosphate. It inhibits (potentially) HBV DNA polymerase and reverse transcriptase. Tenofovir, one of the main components in antiretroviral regimens, plays a key role in HIV treatment. It is also a highly potent inhibitor of HBV DNA replication and recommended as a first-line treatment choice in CHB by the current clinical guidelines due to the absence of resistance to the drug[1,70]. The molecular structure and general safety profile of tenofovir is similar to adefovir, but nephrotoxicity has not been a major problem with tenofovir at therapeutic doses. Therefore, it can be used at higher doses compared to adefovir and leads to more effective responses in HBV DNA decline. The nephrotoxic effect of tenofovir is discussed in detail in the below section on "Renal Safety of NAs".

In phase Ⅲ studies of tenofovir, the adverse event profiles were similar to those in the comparative arm of adefovir. The most frequent adverse events were headache, nasopharyngitis, back pain and nausea. Treatment-related adverse events were detected in 6% of patients, serious adverse events in 4% and adverse events that required discontinuation of tenofovir in less than 1%[8,55]. A 3-year, prospective real-world study (Vireal group) reported 68 adverse events in 41 (9.3%) patients among a total of 440 patients receiving tenofovir. Adverse events occurring in more than one patient were renal disorders (n = 11), abdominal pain (n = 8), asthenia (n = 7), nausea (n = 6), vomiting (n = 5) and diarrhea (n = 5). Nine of the 16 serious side effects were reported to be tenofovir-related (visual impairment, nausea, asthenia gait disturbance, weight loss, depression, muscular weakness, muscular pain and psoriasis)[71].

Osteomalacia can occur during long-term tenofovir treatment. In randomized clinical trials, a great loss of bone mineral density (BMD) had been well-described in patients with HIV infection treated with tenofovir[55,72-74]. However, tenofovir-related bone fractures were not reported in patients with HBV monoinfection[55]. During the 3-year prospective follow-up, fractures were observed in 1% of 375 HBeAg-negative and 266 HBeAg-positive patients, but none were related to tenofovir[75]. The primary responsible mechanism for bone density loss is believed to be related with inhibitory effects of HIV proteins or immune status in osteoblasts and an increased osteoclastic activity. Modifying effects of tenofovir on osteoblast gene expression and function was the other mechanism defined in recent reports[72]. The exact mechanism of bone toxicity in CHB is not clear. Possibly, proximal tubular damage caused by TDF therapy leads to hypophosphatemia and, indirectly, to inadequate mineralization of bone matrix[3]. There have been case reports regarding tenofovir-associated osteomalacia. A recent study including 170 patients with CHB infection compared patients treated with tenofovir (n = 122) and control patients (n = 48) in terms of bone health[72]. The prevalence of BMD loss in patients receiving tenofovir was similar to those who were not exposed to tenofovir. Tenofovir was reported to be associated with a lower T score only in the hips. Additionally, in the study, there was no significant correlation between duration of exposure to tenofovir and reduction in BMD at any side. The risk factors for reduction in BMD other than tenofovir exposure were the known classical factors including advancing age, lower body mass index and smoking[72-74]. A large retrospective study including 53500 subjects in Hong Kong (46454 untreated and 7046 treated) investigated renal and bone events in CHB patients with and without NAs. The patients treated with NAs had similar risk of hip fracture, spine fracture and all fracture, compared to untreated CHB patients. Treatment with nucleotide analogues, compared to nucleoside analogues, was found to increase only the risk of hip fracture but not the other side fracture, and the overall fracture rate was low[76]. Additionally, BMD reduction was demonstrated to remain constant on a plateau from year 4 through year 7 of tenofovir treatment, for both hip and lumbar spine[77]. Thus, we may conclude that

BMD reduction is not a progressive event and is detected in the first years of treatment[78]. These are important findings due to CHB infection requiring lifelong treatment in the majority of patients because the discontinuation of NAs after sustained viral response have a high risk of relapse. Tenofovir can be preferred and used safely in CHB patients in the long-term. Nevertheless, BMD should be periodically performed in patients with CHB infection treated with tenofovir[79]. Osteoporotic patients, especially with advanced age and smoking history, should be monitored more closely and, if required, consulted with a physical rehabilitation specialist.

RENAL SAFETY OF NAs

The adverse effect of NAs on renal function is an important issue that should be carefully evaluated, since HBV infection alone carries an increased risk of renal impairment[80]. All NAs are excreted through kidneys in unchanged forms and some of them are associated with dose-dependent nephrotoxicity[3]. Nephrotoxicity results from proximal tubular damage and presents with elevated serum creatinine, proteinuria, nephrogenic diabetes insipidus, hypophosphatemia or the more severe form, Fanconi syndrome[15]. Mauss *et al*[81] reported a milder decrease in renal function with CHB therapy irrespective of medications. Comorbidities such as diabetes, hypertension and underlying chronic renal disease may also contribute to the nephrotoxic effect of NAs and aggravate renal dysfunction. In a study analyzing effects of NAs and comorbidities on renal function in 4178 CHB patients, age, diabetes, chronic renal disease, renal transplantation and simultaneous administration of diuretics were found to be independent risk factors for the rapid progression of renal disease[81].

Renal toxicity is the most noticeable side effect of adefovir. It is generally dose- and time-dependent, and reversible with dose-adjustment or discontinuation of the drug[15,45,82-84]. In the majority of studies, nephrotoxicity was defined as an increase $\geqslant$ 0.5 mg/dL from baseline in serum creatinine or a serum phosphorus value of $<$ 1.5 mg/dL on two consecutive occasions[83]. In previous studies, including randomized controlled ones, adefovir at 30 mg/d was reported to be nephrotoxic, but adefovir at 10 mg/d was well tolerated and did not lead to an increase in renal dysfunction compared to placebo[45,85]. In a study including a total of 515 patients with CHB, three groups who were treated placebo (n = 170), adefovir dipivoxil at 10 mg (n = 172) or adefovir dipivoxil at 30 mg (n = 173) were compared in terms of response to the treatment and adverse events rates[45]. The safety profile was similar in two groups, the placebo group and the adefovir dipivoxil at 10 mg per day group. There was no significant change in median serum creatinine level at wk 48 of the treatment in these groups. However, 8% of the 30-mg group experienced an increase from baseline of 0.5 mg/dL (44 μmol/L) or greater in the serum creatinine level. The prolonged use of adefovir carries an extra risk of renal dysfunction. The incidences of increased creatinine level and hypophosphatemia were reported to be increased with longer usage of adefovir, even in patients receiving standard low-dose drug.

In recent years, Fanconi syndrome cases due to long-term use of adefovir have been increasingly reported, especially in East Asian populations[83]. Fanconi syndrome is defined as hypophosphatemia and a slight increase in serum creatinine, resulting in proximal renal tubular dysfunction. Additionally, osteomalacia may develop secondary to hypophosphatemia. The patient's main symptoms can be muscular weakness and bone pain involving the knees, ankles and ribs. Clinicians should be aware of this potential complication and monitor periodically the renal function and serum phosphate level in any patient receiving adefovir[83,86]. In a current meta-analysis, including seven randomized controlled trials, four cohort studies and six single-arm studies, adefovir treatment was not found to be associated with increased nephrotoxicity in the randomized controlled trials. However, the cohort studies showed an increased nephrotoxicity risk in patients given adefovir, and the single-arm studies revealed an approximately 1.7-fold increased risk of renal dysfunction in patients given adefovir compared to those treated with all other NAs[82]. The authors drew attention to the differences between the risk of nephrotoxicity in randomized controlled trials and cohort studies and emphasized that since the randomized controlled trials were small-sized and short observational studies, the safety data may be inadequate and that these studies may have underestimated the adverse events. Current evidence indicated an increased risk of nephrotoxicity in CHB patients treated with adefovir.

The mechanism of adefovir nephrotoxicity was poorly understood. Nephrotoxicity may result from the apoptotic or mitochondrial toxic effect of adefovir in the renal tubular epithelium. The deterioration of the balance between the active adefovir uptake from blood into proximal tubular cells, the secretion into urine, and accumulation in proximal tubular cells represent the primary mechanism of tubular toxicity.

Fanconi syndrome is a rare but serious adverse effect of adefovir treatment. Fanconi syndrome is characterized by proximal renal tubular toxicity and leads to increased urinary excretion of amino acids, uric acid, bicarbonate, glucose and phosphate, and impaired reabsorption of these solutes. Clinical manifestations in adults include polyuria, polydipsia, dehydration and osteomalacia[87]. There are a significant number of cases of adefovir-associated Fanconi syndrome in the literature. Most cases occurred after prolonged use of the drug and resolved after cessation of adefovir or switching to another NA. The lowest dose of adefovir (10 mg) can also lead to Fanconi syndrome[88]. Normalization of creatinine level may require more than 1 year. In a retrospective case series study including 35 patients with Fanconi syndrome, hypophosphatemia, increased urinary phosphate excretion and elevated alkaline phosphatase were detected in all patients.

Although serum phosphate levels rapidly increased, especially within the 4 wk after adefovir discontinuation, serum creatinine levels did not decrease to normal range even 1 year after discontinuation of therapy[88]. Fanconi syndrome was rare in CHB patients treated with tenofovir; it has been reported especially in cases of HIV-HBV coinfection[87,89-91].

Despite tenofovir being a higher dose preparation (300 mg/d) that has similar molecular structure with adefovir, renal toxicity has been less commonly detected[3]. In animal studies, tenofovir was reported to be associated with renal dysfunction[3,84]. The mechanism of nephrotoxicity is poorly understood, but it may involve proximal tubular damage, mitochondrial toxicity and apoptosis[8,92].

Tenofovir has been shown to have a potential nephrotoxic effect in patients with HIV infection who were treated for an especially extended period. However, in clinical trials, nephrotoxicity does not seem to be a major problem in HBV monoinfection[3,55,93]. Increases in serum creatinine of > 0.5 mg/dL were reported to be detected in 1% of patients and remained stable over 4 years in less than 1% of patients, with increased serum creatinine levels of 0.5 mg/dL[93]. Nevertheless, renal functions and serum phosphate should be monitored regularly in patients treated with tenofovir[3].

In a study conducted by the Vireal group, a slight decrease of mean glomerular filtration rate (GFR) was reported during tenofovir therapy. Median change in creatinine clearance and serum creatinine level remained stable over time. Of the patients, 15% (n = 65) had a decline in GFR of ≥ 20% and 6% (n = 26) had a decline in GFR of ≥ 30% compared to baseline. Tenofovir treatment was discontinued in 23 patients due to adverse events. Seven of them were associated with renal disorders (n = 3, renal failures; n = 2, renal impairments; n = 2, renal tubular disorders)[71]. Patients who have an underlying renal impairment or HIV coinfection and those who receive a nephrotoxic drug are at increased risk of nephrotoxicity. In a study comparing tenofovir and entecavir in the same number of patients, diabetes and transplantation but not tenofovir treatment were found to be associated with increased risk of renal impairment[94]. A significant number of studies reported that tenofovir did not lead to clinically relevant changes in renal function[79,95].

In a prospective open-label study, conducted by Heathcote *et al*[75], creatinine and creatinine clearance were reported to remain stable during a 3-year period, with a change in creatinine of 0.02 mg/dL at week 144. Two patients experienced a 0.5 mg/dL increase in creatinine and 4 patients a reduction in serum phosphorus < 2 mg/dL. All patients remained in the study and continued the tenofovir therapy. The long-term follow-up results of tenofovir therapy support the previous data. At year 6, less than 1.5% experienced impairment in renal function (≥ 0.5 mg/dL increase in serum creatinine from baseline, phosphorus < 2 mg/dL, or CrCL < 50 mL/min) with tenofovir treatment[55]. Recently, Buti *et al*[77] reported 7th year results of tenofovir treatment for CHB. Of 585 patients, 21 (3.6%) experienced renal function impairment. A serum creatinine increase ≥ 0.5 mg/dL above baseline were confirmed in only 10 patients (1.7%). The patients who did and did not develop renal insufficiency were statistically different in terms of mean age (47 years *vs* 40 years; P = 0.003), baseline mean creatinine clearance (98.5 mL/min *vs* 117.4 mL/min; P = 0.003) and main serum phosphate (2.8 mg/dL *vs* 3.3 mg/dL; P = 0.002). Despite the absence of significant evidence that tenofovir is a nephrotoxic agent, possible proximal tubular damage should still be kept in mind[3]. The patients with normal renal function or mild renal impairment who have no increased risk for renal toxicity should be monitored every 6 mo for serum creatinine and phosphorus. The patients with impaired renal function or underlying comorbidities that show increased renal failure may be monitored more frequently[96]. Dose-adjustment should be made according to the renal impairment[3].

Tenofovir safety was also similar in elderly and younger patients[59]. There is little experience with tenofovir treatment in renal transplantation. One study reported 7 HBV-positive organ transplant recipients (n = 3, kidney; n = 1, liver; n = 3, hearts) who were safely and effectively treated with tenofovir. No adverse events or kidney rejection were observed. There were no statistically significant changes in renal functions[97].

In contrast to the nucleotide analogues, nucleoside analogues are not generally associated with renal adverse events. Increase in serum creatinine was reported in less than 1% of patients treated with entecavir[49]. In the study of Tsai *et al*[98], entecavir and telbivudine were found to be associated with GFR improvement. Despite the absence of strong evidence, the current guidelines recommend entecavir as the best option in renal transplant recipients due to lack of data demonstrating a major renal toxicity with entecavir[2,99-101].

Interestingly, telbivudine improves renal functions[3,8,81]. Several real-life studies have shown that treatment with telbivudine increases GFR in CHB patients. The GLOBE study and long-term extension studies had revealed that long-term telbivudine treatment was associated with a sustained improvement in renal function in patients with compensated and decompensated cirrhosis who had an increased risk of renal impairment[23,102]. Gane *et al*[102] indicated an improvement in renal function with telbivudine treatment by the calculation of GFR using the Modification of Diet in Renal Disease, Chronic Kidney Disease Epidemiology Collaboration, and Cockcroft-Gault methods. The increment of GFR was also shown in patients at increased risk for renal impairment: +17.2% in patients with baseline GFR of 60-89 mL/min per 1.73 m^2, +11.4% in patients older than 50 years and +7.2% in cirrhotic patients. Additionally, improved renal function has been reported to be maintained for 4-6 years. In a study investigating the renoprotective effect of telbivudine on patients receiving adefovir-based combination therapy, combination of adefovir and telbivudine was found to have a more protective effect on renal functions than the combination of adefovir and entecavir, combination of adefovir and lamivudine, adefovir alone or entecavir alone[79]. Preemptive telbivudine use was reported to prevent renal deterioration caused by cisplatin-based chemotherapy in patients with advanced HCC[103]. Additionally, telbivudine is recommended in the prophylactic treatment of CHB in patients with renal transplant due to its renoprotective effect on transplanted patients[2]. Telbivudine is a good option, especially in patients with renal impairment or in those with risk factors for renal disease.

All NAs are cleared by kidneys and their dosage should be adjusted in patients with creatinine clearance below 50 mL/min[104]. To minimize the risk of nephrotoxicity, simultaneous administration of the other nephrotoxic drugs should be avoided. Secondly, all patients with CHB infection who are treated with adefovir or tenofovir should be regularly monitored for serum creatinine and phosphate levels and drug dose should be modified if creatinine increases by more than 0.5 mg/dL above baseline or phosphate level decreases below 2.0 mg/dL, to the needed dose[8].

SAFETY IN PREGNANCY

Mother-to-child-transmission remains the main route of hepatitis B acquisition, especially in endemic countries[105]. Despite postnatal use of immune globulin and vaccine, mother-to-child transmission of HBV infection still occurs. Intrauterine transmission is considered the main reason underlying immunoprophlaxis failures[2,106]. High HBV DNA levels and HBeAg-positive status are the most important risk factors for perinatal HBV transmission. Thus, reducing maternal HBV DNA level has become the main preventive measure of perinatal mother-to-child transmission[106]. Current guidelines recommend initiating NAs in pregnant females with high HBV DNA levels (above > 10^{6-7} IU/mL) at 28-32 wk of gestation and cessation of NAs after delivery or 4-12 wk after delivery in females who do not have a risk for ALT flares and pre-existing advanced liver fibrosis/cirrhosis[2,105].

Two of five NAs approved for the treatment of CHB, telbivudine and tenofovir, are classified as category B in the United States FDA Pregnancy Categories (meaning that no risk was observed in animal studies; however, there are no adequate and well-controlled studies performed in pregnant women). The other three NAs, lamivudine, entecavir and adefovir, are classified as category C (meaning that an adverse effect on the fetus have been shown in animal studies, but there are no adequate studies in humans)[107] (Table 1). Prospective studies have revealed that fetal abnormality rates in mothers treated with NAs is low, and similar to those in the general population[3]. Lamivudine is the most experienced NA in pregnancy and it has been used safely in preventing mother-to-child transmission of HIV infection for 2 decades[2]. In randomized controlled studies, lamivudine has been shown to be effective in preventing mother-to-child-transmission when used in the third trimester of pregnancy and early postnatal period. There was no significant difference in the incidence of fetal adverse effects between lamivudine and placebo groups[108,109]. The Antiretroviral Pregnancy Registry (APR) provides updated fetal safety data on various drugs used in pregnancy, and includes data from January 1989 to date. Up to 31 July 2015, APR reported newborn defect rates as 3.1% during the first trimester of 4566 pregnant women and 2.9% during the second/third trimester of 7263 pregnant women who were exposed to lamivudine. These rates were not different from those reported in the general population[110]. However, lamivudine administration, even if for short-term use such as during pregnancy, has a risk of selecting resistant strains due to poor antiviral activity[106]. Current guidelines do not recommend lamivudine as first-line therapy for the treatment of CHB infection in pregnant women[1,2].

Tenofovir is recommended in current guidelines for preventing mother-to-child transmission in pregnant women with high viremia based on its potent antiviral activity, high barrier to resistance and being safe[1,2]. Data on tenofovir safety has been usually obtained from patients with HIV infection. It has been safely used in pregnant women with HIV infection for a relatively long time. APR reported newborn defect rates as 2.3% during the first trimester of 2608 pregnant women and 2.1% during the second/third trimester of 1258 pregnant women, which is similar to the rates in the general population. In a retrospective study, conducted in 45 HBeAg-positive pregnant women with high HBV DNA levels, tenofovir was found to be effective in preventing vertical transmission and no significant fetal adverse events were observed[111]. The other multi-center prospective observational study reported tenofovir to be more effective than lamivudine in preventing vertical transmission[112]. These data are supported by other studies[113].

Telbivudine has greater potency than lamivudine in decreasing HBV DNA level and it is recommended by current guidelines in the prevention of mother-to-child transmission of HBV infection. Use of telbivudine during the second/third trimester of pregnancy was reported to be effective and safe. Compared to placebo, no serious adverse events were found in telbivudine-treated mothers and their infants[3,12]. Despite the relatively low resistance rate compared to lamivudine, telbivudine resistance may occur during therapy[105]. There are no adequate and well-controlled studies on the safety profile of entecavir and adefovir in pregnant women infected with CHB[15].

Breast-feeding is discouraged during maternal NAs treatment due to the uncertain safety on infants[1,2]. Lamivudine is concentrated in breast milk. However, its amount in infants exposed to lamivudine during breast-feeding is accepted to be insignificant (approximately 2% of the recommended daily treatment dose)[114]. Similarly, tenofovir concentrations in breast milk have been reported, but infants are exposed to a small amount because its oral bioavailability is limited[1]. There is no adequate evidence to recommend the use of entecavir and adefovir during the breast-feeding period[110,111]. Lamivudine or tenofovir is regarded as the choice in breastfeeding mothers who needed to receive treatment for HBV infection.

CONCLUSION

In light of the current data, the treatment of CHB seems to be a life-long therapy. Thus, the long-term safety of the drugs is one of the main factors that influence treatment decision. To date, five oral NAs have been approved for the treatment of CHB. All NAs are generally safe and well-tolerated by CHB patients. All NAs carry a "Black Box" warning about mitochondrial dysfunction. The majority of mitochondrial toxicity cases are associated with lamivudine and telbivudine and generally present as myopathy, neuropathy or lactic acidosis. No increased incidence of myopathy was reported with adefovir, tenofovir and entecavir treatment, compared to placebo. Adefovir is a well-known nephrotoxic agent and may cause renal proximal tubular dysfunction. Fanconi syndrome cases have been increasingly reported in long-term adefovir therapy. Tenofovir has potential nephrotoxic and bone density loss effects, especially in patients with HIV coinfection. Entecavir and lamivudine are not generally associated with renal adverse events. Interestingly, telbivudine has the effect of improving renal function. Serum creatinine, phosphorus and CK levels should be monitored, especially in patients treated with adefovir and tenofovir. Since BMD reduction may occur during tenofovir treatment, BMD measurements should be periodically performed. Although entecavir is suggested to be associated with lactic acidosis in CHB patients with high MELD scores, its use in compensated and decompensated cirrhotic patients were reported to be safe. Safety profile is a major issue that should not be ignored in the treatment of CHB. Further studies should be done to clarify the adverse effects of NAs and determine follow-up timing and frequency, especially in selected patient populations including those with HIV-coinfection or renal impairment, and pregnant or breastfeeding women.

Prolonged treatment experience can still reveal some unknown adverse effects of drugs. Clinical trial data in different patient populations continue to accumulate in the literature. This review contains updated comprehensive data about the safety profile of NAs used in CHB.

REFERENCES

1 **Sarin SK**, Kumar M, Lau GK, Abbas Z, Chan HL, Chen CJ, Chen DS, Chen HL, Chen PJ, Chien RN, Dokmeci AK, Gane E, Hou JL, Jafri W, Jia J, Kim JH, Lai CL, Lee HC, Lim SG, Liu CJ, Locarnini S, Al Mahtab M, Mohamed R, Omata M, Park J, Piratvisuth T, Sharma BC, Sollano J, Wang FS, Wei L, Yuen MF, Zheng SS, Kao JH. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepatol Int* 2016; **10**: 1-98 [PMID: 26563120 DOI: 10.1007/s12072-015-9675-4]

2 **European Association for the Study of Liver.** EASL clinical practical guidelines: management of alcoholic liver disease. *J Hepatol* 2012; **57**: 399-420 [PMID: 22633836 DOI: 10.1016/j.jhep.2012.04.004]

3 **Fung J**, Lai CL, Seto WK, Yuen MF. Nucleoside/nucleotide analogues in the treatment of chronic hepatitis B. *J Antimicrob Chemother* 2011; **66**: 2715-2725 [PMID: 21965435 DOI: 10.1093/jac/dkr388]

4 **Newbold JE**, Xin H, Tencza M, Sherman G, Dean J, Bowden S, Locarnini S. The covalently closed duplex form of the hepadnavirus genome exists in situ as a heterogeneous population of viral minichromosomes. *J Virol* 1995; **69**: 3350-3357 [PMID: 7745682]

5 **Fung J**, Seto WK, Lai CL, Yuen MF. Extrahepatic effects of nucleoside and nucleotide analogues in chronic hepatitis B treatment. *J Gastroenterol Hepatol* 2014; **29**: 428-434 [PMID: 24372662 DOI: 10.1111/jgh.12499]

6 **Shan C**, Yin GQ, Wu P. Efficacy and safety of tenofovir in a kidney transplant patient with chronic hepatitis B and nucleos(t)ide multidrug resistance: a case report. *J Med Case Rep* 2014; **8**: 281 [PMID: 25146249 DOI: 10.1186/1752-1947-8-281]

7 **Petersen J**, Buti M. Considerations for the long-term treatment of chronic hepatitis B with nucleos(t)ide analogs. *Expert Rev Gastroenterol Hepatol* 2012; **6**: 683-693; quiz 694 [PMID: 23237254 DOI: 10.1586/egh.12.52]

8 **Fontana RJ**. Side effects of long-term oral antiviral therapy for hepatitis B. *Hepatology* 2009; **49**: S185-S195 [PMID: 19399802 DOI: 10.1002/hep.22885]

9 **Wolters LM**, Niesters HG, de Man RA. Nucleoside analogues for chronic hepatitis B. *Eur J Gastroenterol Hepatol* 2001; **13**: 1499-1506 [PMID: 11742201]

10 **Marcellin P**, Wursthorn K, Wedemeyer H, Chuang WL, Lau G, Avila C, Peng CY, Gane E, Lim SG, Fainboim H, Foster GR, Safadi R, Rizzetto M, Manns M, Bao W, Trylesinski A, Naoumov N. Telbivudine plus pegylated interferon alfa-2a in a randomized study in chronic hepatitis B is associated with an unexpected high rate of peripheral neuropathy. *J Hepatol* 2015; **62**: 41-47 [PMID: 25152207 DOI: 10.1016/j.jhep.2014.08.021]

11 **Martin JL**, Brown CE, Matthews-Davis N, Reardon JE. Effects of antiviral nucleoside analogs on human DNA polymerases and mitochondrial DNA synthesis. *Antimicrob Agents Chemother* 1994; **38**: 2743-2749 [PMID: 7695256]

12 **Fleischer RD**, Lok AS. Myopathy and neuropathy associated with nucleos(t)ide analog therapy for hepatitis B. *J Hepatol* 2009; **51**: 787-791 [PMID: 19665816 DOI: 10.1016/j.jhep.2009.06.011]

13 **Kim BK**, Oh J, Kwon SY, Choe WH, Ko SY, Rhee KH, Seo TH, Lim SD, Lee CH. Clevudine myopathy in patients with chronic hepatitis B. *J Hepatol* 2009; **51**: 829-834 [PMID: 19615776 DOI: 10.1016/j.jhep.2009.04.019]

14 **Tak WY**, Park SY, Cho CM, Jung MK, Jeon SW, Kweon YO, Park JY, Sohn YK. Clinical, biochemical, and pathological characteristics of clevudine-associated myopathy. *J Hepatol* 2010; **53**: 261-266 [PMID: 20466447 DOI: 10.1016/j.jhep.2010.03.006]

15 **Mak LY**, Seto WK, Lai CL, Yuen MF. DNA polymerase inhibitors for treating hepatitis B: a safety evaluation. *Expert Opin Drug Saf* 2016; **15**: 383-392 [PMID: 26752687 DOI: 10.1517/14740338.2016.1139573]

16 **Xu H**, Wang Z, Zheng L, Zhang W, Lv H, Jin S, Yuan Y. Lamivudine/telbivudine-associated neuromyopathy: neurogenic damage, mitochondrial dysfunction and mitochondrial DNA depletion. *J Clin Pathol* 2014; **67**: 999-1005 [PMID: 25190818 DOI: 10.1136/jclinpath-2013-202069]

17 **Wang M**, Da Y, Cai H, Lu Y, Wu L, Jia J. Telbivudine myopathy in a patient with chronic hepatitis B. *Int J Clin Pharm* 2012; **34**: 422-425 [PMID: 22527478 DOI: 10.1007/s11096-012-9633-3]

18 **Shin SR**, Yoo BC, Choi MS, Lee DH, Song SM, Lee JH, Koh KC, Paik SW. A comparison of 48-week treatment efficacy between clevudine and entecavir in treatment-naïve patients with chronic hepatitis B. *Hepatol Int* 2011; **5**: 664-670 [PMID: 21484144 DOI: 10.1007/s12072-010-9238-7]

19 **Yuan K**, Guochun W, Huang Z, Lin B, Zhou H, Lu X. Entecavir-associated myopathy: a case report and literature review. *Muscle Nerve* 2014; **49**: 610-614 [PMID: 24218312 DOI: 10.1002/mus.24118]
20 **Palumbo E**. Lamivudine for chronic hepatitis B: a brief review. *Braz J Infect Dis* 2008; **12**: 355-357 [PMID: 19219271]
21 **Leung N**. Treatment of chronic hepatitis B: case selection and duration of therapy. *J Gastroenterol Hepatol* 2002; **17**: 409-414 [PMID: 11982721]
22 **Leung NW**, Lai CL, Chang TT, Guan R, Lee CM, Ng KY, Lim SG, Wu PC, Dent JC, Edmundson S, Condreay LD, Chien RN; Asia Hepatitis Lamivudine Study Group. Extended lamivudine treatment in patients with chronic hepatitis B enhances hepatitis B e antigen seroconversion rates: results after 3 years of therapy. *Hepatology* 2001; **33**: 1527-1532 [PMID: 11391543]
23 **Liaw YF**, Gane E, Leung N, Zeuzem S, Wang Y, Lai CL, Heathcote EJ, Manns M, Bzowej N, Niu J, Han SH, Hwang SG, Cakaloglu Y, Tong MJ, Papatheodoridis G, Chen Y, Brown NA, Albanis E, Galil K, Naoumov NV; GLOBE Study Group. 2-Year GLOBE trial results: telbivudine Is superior to lamivudine in patients with chronic hepatitis B. *Gastroenterology* 2009; **136**: 486-495 [PMID: 19027013 DOI: 10.1053/j.gastro.2008.10.026]
24 **Lok AS**, Lai CL, Leung N, Yao GB, Cui ZY, Schiff ER, Dienstag JL, Heathcote EJ, Little NR, Griffiths DA, Gardner SD, Castiglia M. Long-term safety of lamivudine treatment in patients with chronic hepatitis B. *Gastroenterology* 2003; **125**: 1714-1722 [PMID: 14724824]
25 **Tillmann HL**, Hadem J, Leifeld L, Zachou K, Canbay A, Eisenbach C, Graziadei I, Encke J, Schmidt H, Vogel W, Schneider A, Spengler U, Gerken G, Dalekos GN, Wedemeyer H, Manns MP. Safety and efficacy of lamivudine in patients with severe acute or fulminant hepatitis B, a multicenter experience. *J Viral Hepat* 2006; **13**: 256-263 [PMID: 16611192]
26 **Roche B**, Samuel D. The difficulties of managing severe hepatitis B virus reactivation. *Liver Int* 2011; **31** Suppl 1: 104-110 [PMID: 21205146 DOI: 10.1111/j.1478-3231.2010.02396.x]
27 **Huprikar S**, Danziger-Isakov L, Ahn J, Naugler S, Blumberg E, Avery RK, Koval C, Lease ED, Pillai A, Doucette KE, Levitsky J, Morris MI, Lu K, McDermott JK, Mone T, Orlowski JP, Dadhania DM, Abbott K, Horslen S, Laskin BL, Mougdil A, Venkat VL, Korenblat K, Kumar V, Grossi P, Bloom RD, Brown K, Kotton CN, Kumar D. Solid organ transplantation from hepatitis B virus-positive donors: consensus guidelines for recipient management. *Am J Transplant* 2015; **15**: 1162-1172 [PMID: 25707744 DOI: 10.1111/ajt.13187]
28 **Wright AJ**, Fishman JA, Chung RT. Lamivudine compared with newer antivirals for prophylaxis of hepatitis B core antibody positive livers: a cost-effectiveness analysis. *Am J Transplant* 2014; **14**: 629-634 [PMID: 24460820 DOI: 10.1111/ajt.12598]
29 **Loomba R**, Rowley A, Wesley R, Liang TJ, Hoofnagle JH, Pucino F, Csako G. Systematic review: the effect of preventive lamivudine on hepatitis B reactivation during chemotherapy. *Ann Intern Med* 2008; **148**: 519-528 [PMID: 18378948]
30 **Liberek A**, Szaflarska-Popławska A, Korzon M, Łuczak G, Góra-Gebka M, Łoś-Rycharska E, Bako W, Czerwionka-Szaflarska M. Lamivudine therapy for children with chronic hepatitis B. *World J Gastroenterol* 2006; **12**: 2412-2416 [PMID: 16688835]
31 **Baharin J**, Sahari NS, Lim SM. Rhabdomyolysis due to Lamivudine administration in acute viral hepatitis B infection: a case report from Malaysia. *Electron Physician* 2014; **6**: 863-867 [PMID: 25763159 DOI: 10.14661/2014.863-86]
32 **Yahagi K**, Ueno Y, Mano Y, Shimosegawa T. Rhabdomyolytic syndrome during the lamivudine therapy for acute exacerbation of chronic type B hepatitis. *Liver Transpl* 2002; **8**: 1198-1199 [PMID: 12474162]
33 **Holt SG**, Moore KP. Pathogenesis and treatment of renal dysfunction in rhabdomyolysis. *Intensive Care Med* 2001; **27**: 803-811 [PMID: 11430535]
34 **Adani GL**, Baccarani U, Risaliti A, Bresadola F, Della Rocca G, Viale P. Rhabdomyolysis due to Lamivudine administration in a liver transplant recipient. *Am J Transplant* 2005; **5**: 634 [PMID: 15707423]
35 **Song X**, Hu Z, Zhang H. Acute dystonia induced by lamivudine. *Clin Neuropharmacol* 2005; **28**: 193-194 [PMID: 16062101]
36 **Kaptanoglu AF**, Kutluay L. Ichthyosiform eruption associated with lamivudine in a patient with chronic hepatitis-B infection. *Int J Clin Pract* 2005; **59**: 1237-1238 [PMID: 16178993]
37 **Tuon FF**, Guastini CM, Boulos MI. Acute pancreatitis associated with lamivudine therapy for chronic B hepatitis. *Braz J Infect Dis* 2008; **12**: 263 [PMID: 19030723]
38 **Soylu AR**, Dökmeci G, Tezel A, Cakir B, Umit H, Karahan N, Amuca H. Lamivudine-induced acute pancreatitis in a patient with decompensated Hbv-related chronic liver disease. *J Clin Gastroenterol* 2004; **38**: 134 [PMID: 14745288]
39 **Matthews SJ**. Telbivudine for the management of chronic hepatitis B virus infection. *Clin Ther* 2007; **29**: 2635-2653 [PMID: 18201580 DOI: 10.1016/j.clinthera.2007.12.032]
40 **Wang YH**, Wu BQ, Liu H. Continuous venovenous hemodiafiltration for hyperlactatemia caused by telbivudine in a patient with chronic hepatitis B: a case report and update review. *J Dig Dis* 2015; **16**: 164-167 [PMID: 25043654 DOI: 10.1111/1751-2980.12173]
41 **Zou XJ**, Jiang XQ, Tian DY. Clinical features and risk factors of creatine kinase elevations and myopathy associated with telbivudine. *J Viral Hepat* 2011; **18**: 892-896 [PMID: 22093034 DOI: 10.1111/j.1365-2893.2010.01412.x]
42 **Zhang XS**, Jin R, Zhang SB, Tao ML. Clinical features of adverse reactions associated with telbivudine. *World J Gastroenterol* 2008; **14**: 3549-3553 [PMID: 18567085]
43 **Jin JL**, Hu P, Lu JH, Luo SS, Huang XY, Weng XH, Zhang JM. Lactic acidosis during telbivudine treatment for HBV: a case report and literature review. *World J Gastroenterol* 2013; **19**: 5575-5580 [PMID: 24023503 DOI: 10.3748/wjg.v19.i33.5575]
44 **Lai CL**, Leung N, Teo EK, Tong M, Wong F, Hann HW, Han S, Poynard T, Myers M, Chao G, Lloyd D, Brown NA; Telbivudine Phase II Investigator Group. A 1-year trial of telbivudine, lamivudine, and the combination in patients with hepatitis B e antigen-positive chronic hepatitis B. *Gastroenterology* 2005; **129**: 528-536 [PMID: 16083710]
45 **Marcellin P**, Chang TT, Lim SG, Tong MJ, Sievert W, Shiffman ML, Jeffers L, Goodman Z, Wulfsohn MS, Xiong S, Fry J, Brosgart CL; Adefovir Dipivoxil 437 Study Group. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. *N Engl J Med* 2003; **348**: 808-816 [PMID: 12606735]
46 **Dando T**, Plosker G. Adefovir dipivoxil: a review of its use in chronic hepatitis B. *Drugs* 2003; **63**: 2215-2234 [PMID: 14498759]
47 **Sokal EM**, Kelly D, Wirth S, Mizerski J, Dhawan A, Frederick D. The pharmacokinetics and safety of adefovir dipivoxil in children and adolescents with chronic hepatitis B virus infection. *J Clin Pharmacol* 2008; **48**: 512-517 [PMID: 18276803 DOI: 10.1177/0091270007313325]
48 **Hadziyannis SJ**, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, Marcellin P, Lim SG, Goodman Z, Wulfsohn MS, Xiong S, Fry J, Brosgart CL; Adefovir Dipivoxil 438 Study Group. Adefovir dipivoxil for the treatment of hepatitis B e antigen-negative chronic hepatitis B. *N Engl J Med* 2003; **348**: 800-807 [PMID: 12606734]
49 **Lange CM**, Bojunga J, Hofmann WP, Wunder K, Mihm U, Zeuzem S, Sarrazin C. Severe lactic acidosis during treatment of chronic hepatitis B with entecavir in patients with impaired liver function. *Hepatology* 2009; **50**: 2001-2006 [PMID: 19937695 DOI: 10.1002/hep.23346]
50 **Kim SB**, Kim SU, Kim BK, Park JY, Kim do Y, Ahn SH, Han KH. Outcome of adefovir add-on lamivudine rescue therapy of up to 5 years in patients with lamivudine-resistant chronic hepatitis B. *J Gastroenterol Hepatol* 2016; **31**: 241-247 [PMID: 26204913 DOI: 10.1111/jgh.13046]
51 **Matthews SJ**. Entecavir for the treatment of chronic hepatitis B virus infection. *Clin Ther* 2006; **28**: 184-203 [PMID: 16678641]
52 **Tangkijvanich P**, Chittmittraprap S, Poovorawan K, Limothai U, Khlaiphuengsin A, Chuaypen N, Wisedopas N, Poovorawan Y. A

randomized clinical trial of peginterferon alpha-2b with or without entecavir in patients with HBeAg-negative chronic hepatitis B: Role of host and viral factors associated with treatment response. *J Viral Hepat* 2016; **23**: 427-438 [PMID: 26387494 DOI: 10.1111/jvh.12467]
53 **Suzuki F**, Toyoda J, Katano Y, Sata M, Moriyama M, Imazeki F, Kage M, Seriu T, Omata M, Kumada H. Efficacy and safety of entecavir in lamivudine-refractory patients with chronic hepatitis B: randomized controlled trial in Japanese patients. *J Gastroenterol Hepatol* 2008; **23**: 1320-1326 [PMID: 18554238 DOI: 10.1111/j.1440-1746.2008.05455.x]
54 **Jonas MM**, Chang MH, Sokal E, Schwarz KB, Kelly D, Kim KM, Ling SC, Rosenthal P, Oraseanu D, Reynolds L, Thiry A, Ackerman P. Randomized, controlled trial of entecavir versus placebo in children with hepatitis B envelope antigen-positive chronic hepatitis B. *Hepatology* 2016; **63**: 377-387 [PMID: 26223345 DOI: 10.1002/hep.28015]
55 **Ridruejo E.** Treatment of chronic hepatitis B in clinical practice with entecavir or tenofovir. *World J Gastroenterol* 2014; **20:** 7169-80 [PMID: 24966587 DOI: 10.3748/wjg.v20.i23.7169]
56 **Mao H**, Kang T. Lactic Acidosis during Entecavir Antiviral Treatment in a Patient with Hepatitis B Virus-related Decompensated Cirrhosis. *West Indian Med J* 2015; **64**: 165-166 [PMID: 26360694 DOI: 10.7727/wimj.2013.198]
57 **Mazzucco CE**, Hamatake RK, Colonno RJ, Tenney DJ. Entecavir for treatment of hepatitis B virus displays no in vitro mitochondrial toxicity or DNA polymerase gamma inhibition. *Antimicrob Agents Chemother* 2008; **52**: 598-605 [PMID: 18056280]
58 **Zhang Y**, Hu P, Qi X, Ren H, Mao RC, Zhang JM. A comparison of telbivudine and entecavir in the treatment of hepatitis B e antigen-positive patients: a prospective cohort study in China. *Clin Microbiol Infect* 2016; **22**: 287.e1-287.e9 [PMID: 26548508 DOI: 10.1016/j.cmi.2015.10.024]
59 **Liang J**, Jiang MJ, Deng X, Xiao Zhou X. Efficacy and Safety of Telbivudine Compared to Entecavir Among HBeAg+ Chronic Hepatitis B Patients: a Meta-Analysis Study. *Hepat Mon* 2013; **13**: e7862 [PMID: 24032045 DOI: 10.5812/hepatmon.7862]
60 **Su QM**, Ye XG. Effects of telbivudine and entecavir for HBeAg-positive chronic hepatitis B: a meta-analysis. *World J Gastroenterol* 2012; **18**: 6290-6301 [PMID: 23180951 DOI: 10.3748/wjg.v18.i43.6290]
61 **Bristol-Myers Squibb**. Baraclude® (entecavir): US prescribing information [online]. [Accessed 2016 Sept 16]. Available from URL: http://packageinserts.bms.com/pi/pi_baraclude.pdf
62 **Gilead Sciences**, Inc. Viread® (tenofovir disoproxil fumarate) tablets: US prescribing information [online]. [Accessed 2016 Sept 16]. Available from URL: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021356s035lbl.pdf
63 **Novartis**. Tyzeka (telbivudine): US prescribing information [online]. [Accessed 2016 Sept 16]. Available from URL: http://www.pharma.us.novartis.com/product/pi/pdf/tyzeka.pdf
64 **Gilead Sciences**, Inc. Hepsera (adefovir dipivoxil) tablets: US prescribing information [online]. [Accessed 2016 Sept 16]. Available from URL: http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021449s016lbl.pdf
65 **Marzano A**, Marengo A, Marietti M, Rizzetto M. Lactic acidosis during Entecavir treatment in decompensated hepatitis B virus-related cirrhosis. *Dig Liver Dis* 2011; **43**: 1027-1028 [PMID: 21782535 DOI: 10.1016/j.dld.2011.06.013]
66 **Keating GM**. Entecavir: a review of its use in the treatment of chronic hepatitis B in patients with decompensated liver disease. *Drugs* 2011; **71**: 2511-2529 [PMID: 22141390 DOI: 10.2165/11208510-000000000-00000]
67 **Liaw YF**, Leung N, Kao JH, Piratvisuth T, Gane E, Han KH, Guan R, Lau GK, Locarnini S; Chronic Hepatitis B Guideline Working Party of the Asian-Pacific Association for the Study of the Liver. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2008 update. *Hepatol Int* 2008; **2**: 263-283 [PMID: 19669255 DOI: 10.1007/s12072-008-9080-3]
68 **Manns MP**, Akarca US, Chang TT, Sievert W, Yoon SK, Tsai N, Min A, Pangerl A, Beebe S, Yu M, Wongcharatrawee S. Long-term safety and tolerability of entecavir in patients with chronic hepatitis B in the rollover study ETV-901. *Expert Opin Drug Saf* 2012; **11**: 361-368 [PMID: 22233350 DOI: 10.1517/14740338.2012.653340]
69 **Chi H**, Arends P, Reijnders JG, Carey I, Brown A, Fasano M, Mutimer D, Deterding K, Oo YH, Petersen J, van Bommel F, de Knegt RJ, Santantonio TA, Berg T, Welzel TM, Wedemeyer H, Buti M, Pradat P, Zoulim F, Hansen BE, Janssen HL. Flares during long-term entecavir therapy in chronic hepatitis B. *J Gastroenterol Hepatol* 2016; **31**: 1882-1887 [PMID: 27008918 DOI: 10.1111/jgh.13377]
70 **Lok AS**, McMahon BJ. Chronic hepatitis B: update 2009. *Hepatology* 2009; **50**: 661-662 [PMID: 19714720 DOI: 10.1002/hep.23190]
71 **Marcellin P**, Zoulim F, Hézode C, Causse X, Roche B, Truchi R, Pauwels A, Ouzan D, Dumortier J, Pageaux GP, Bourlière M, Riachi G, Zarski JP, Cadranel JF, Tilliet V, Stern C, Pétour P, Libert O, Consoli SM, Larrey D. Effectiveness and Safety of Tenofovir Disoproxil Fumarate in Chronic Hepatitis B: A 3-Year, Prospective, Real-World Study in France. *Dig Dis Sci* 2016; **61**: 3072-3083 [PMID: 26821154]
72 **Gill US**, Zissimopoulos A, Al-Shamma S, Burke K, McPhail MJ, Barr DA, Kallis YN, Marley RT, Kooner P, Foster GR, Kennedy PT. Assessment of bone mineral density in tenofovir-treated patients with chronic hepatitis B: can the fracture risk assessment tool identify those at greatest risk? *J Infect Dis* 2015; **211**: 374-382 [PMID: 25156561 DOI: 10.1093/infdis/jiu471]
73 **Perrot S**, Aslangul E, Szwebel T, Caillat-Vigneron N, Le Jeunne C. Bone pain due to fractures revealing osteomalacia related to tenofovir-induced proximal renal tubular dysfunction in a human immunodeficiency virus-infected patient. *J Clin Rheumatol* 2009; **15**: 72-74 [PMID: 19265350 DOI: 10.1097/RHU.0b013e31819c20d8]
74 **Bedimo R**, Maalouf NM, Zhang S, Drechsler H, Tebas P. Osteoporotic fracture risk associated with cumulative exposure to tenofovir and other antiretroviral agents. *AIDS* 2012; **26**: 825-831 [PMID: 22301411 DOI: 10.1097/QAD.0b013e32835192ae]
75 **Heathcote EJ**, Marcellin P, Buti M, Gane E, De Man RA, Krastev Z, Germanidis G, Lee SS, Flisiak R, Kaita K, Manns M, Kotzev I, Tchernev K, Buggisch P, Weilert F, Kurdas OO, Shiffman ML, Trinh H, Gurel S, Snow-Lampart A, Borroto-Esoda K, Mondou E, Anderson J, Sorbel J, Rousseau F. Three-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B. *Gastroenterology* 2011; **140**: 132-143 [PMID: 20955704 DOI: 10.1053/j.gastro.2010.10.011]
76 **Wong GL**, Tse YK, Wong VW, Yip TC, Tsoi KK, Chan HL. Long-term safety of oral nucleos(t)ide analogs for patients with chronic hepatitis B: A cohort study of 53,500 subjects. *Hepatology* 2015; **62**: 684-693 [PMID: 25973979 DOI: 10.1002/hep.27894]
77 **Buti M**, Tsai N, Petersen J, Flisiak R, Gurel S, Krastev Z, Schall RA, Flaherty JF, Martins EB, Charuworn P, Kitrinos KM, Subramanian GM, Gane E, Marcellin P. Seven-year efficacy and safety of treatment with tenofovir disoproxil fumarate for chronic hepatitis B virus infection. *Dig Dis Sci* 2015; **60**: 1457-1464 [PMID: 25532501 DOI: 10.1007/s10620-014-3486-7]
78 **Fung S**, Kwan P, Fabri M, Horban A, Pelemis M, Hann HW, Gurel S, Caruntu FA, Flaherty JF, Massetto B, Dinh P, Corsa A, Subramanian GM, McHutchison JG, Husa P, Gane E. Randomized comparison of tenofovir disoproxil fumarate vs emtricitabine and tenofovir disoproxil fumarate in patients with lamivudine-resistant chronic hepatitis B. *Gastroenterology* 2014; **146**: 980-988 [PMID: 24368224 DOI: 10.1053/j.gastro.2013.12.028]
79 **Ridruejo E**, Silva MO. Safety of long-term nucleos(t)ide treatment in chronic hepatitis B. *Expert Opin Drug Saf* 2012; **11**: 357-360 [PMID: 22417072 DOI: 10.1517/14740338.2012.672972]
80 **Shin JH**, Kwon HJ, Jang HR, Lee JE, Gwak GY, Huh W, Jung SH, Lee JH, Kim YG, Kim DJ, Oh HY. Risk Factors for Renal Functional Decline in Chronic Hepatitis B Patients Receiving Oral Antiviral Agents. *Medicine* (Baltimore) 2016; **95**: e2400 [PMID: 26735542 DOI: 10.1097/MD.0000000000002400]
81 **Mauss S**, Berger F, Filmann N, Hueppe D, Henke J, Hegener P,

Athmann C, Schmutz G, Herrmann E. Effect of HBV polymerase inhibitors on renal function in patients with chronic hepatitis B. *J Hepatol* 2011; **55**: 1235-1240 [PMID: 21703180 DOI: 10.1016/j.jhep.2011.03.030]
82 **Yang Q**, Shi YU, Yang Y, Lou G, Lv F. Association between adefovir dipivoxil treatment and the risk of renal insufficiency in patients with chronic hepatitis B: A meta-analysis. *Biomed Rep* 2015; **3**: 269-275 [PMID: 25798251]
83 **Eguchi H**, Tsuruta M, Tani J, Kuwahara R, Hiromatsu Y. Hypophosphatemic osteomalacia due to drug-induced Fanconi's syndrome associated with adefovir dipivoxil treatment for hepatitis B. *Intern Med* 2014; **53**: 233-237 [PMID: 24492692]
84 **Chen G**, Lin W, Shen F, Iloeje UH, London WT, Evans AA. Past HBV viral load as predictor of mortality and morbidity from HCC and chronic liver disease in a prospective study. *Am J Gastroenterol* 2006; **101**: 1797-1803 [PMID: 16817842]
85 **Izzedine H**, Hulot JS, Launay-Vacher V, Marcellini P, Hadziyannis SJ, Currie G, Brosgart CL, Westland C, Arterbrun S, Deray G; Adefovir Dipivoxil International 437 Study Group; Adefovir Dipivoxil International 438 Study Group. Renal safety of adefovir dipivoxil in patients with chronic hepatitis B: two double-blind, randomized, placebo-controlled studies. *Kidney Int* 2004; **66**: 1153-1158 [PMID: 15327411]
86 **Girgis CM**, Wong T, Ngu MC, Emmett L, Archer KA, Chen RC, Seibel MJ. Hypophosphataemic osteomalacia in patients on adefovir dipivoxil. *J Clin Gastroenterol* 2011; **45**: 468-473 [PMID: 20661153 DOI: 10.1097/MCG.0b013e3181e12ed3]
87 **Samarkos M**, Theofanis V, Eliadi I, Vlachogiannakos J, Polyzos A. Tenofovir-associated Fanconi syndrome in a patient with chronic hepatitis B. *J Gastrointestin Liver Dis* 2014; **23**: 342 [PMID: 25267967]
88 **Xu LJ**, Jiang Y, Liao RX, Zhang HB, Mao JF, Chi Y, Li M, Wang O, Liu XQ, Liu ZY, Xing XP, Yu W, Xia WB. Low-dose adefovir dipivoxil may induce Fanconi syndrome: clinical characteristics and long-term follow-up for Chinese patients. *Antivir Ther* 2015; **20**: 603-611 [PMID: 25814481 DOI: 10.3851/IMP2954]
89 **Viganò M**, Brocchieri A, Spinetti A, Zaltron S, Mangia G, Facchetti F, Fugazza A, Castelli F, Colombo M, Lampertico P. Tenofovir-induced Fanconi syndrome in chronic hepatitis B monoinfected patients that reverted after tenofovir withdrawal. *J Clin Virol* 2014; **61**: 600-603 [PMID: 25453573 DOI: 10.1016/j.jcv.2014.09.016]
90 **Gracey DM**, Snelling P, McKenzie P, Strasser SI. Tenofovir-associated Fanconi syndrome in patients with chronic hepatitis B monoinfection. *Antivir Ther* 2013; **18**: 945-948 [PMID: 23839869 DOI: 10.3851/IMP2649]
91 **Gómez Martinez MV**, Gallardo FG, Pirogova T, García-Samaniego J. Bone scintigraphy and secondary osteomalacia due to nephrotoxicity in a chronic hepatitis B patient treated with tenofovir. *Rev Esp Med Nucl Imagen Mol* 2014; **33**: 103-105 [PMID: 23920225 DOI: 10.1016/j.remn.2013.05.011]
92 **Karras A**, Lafaurie M, Furco A, Bourgarit A, Droz D, Sereni D, Legendre C, Martinez F, Molina JM. Tenofovir-related nephrotoxicity in human immunodeficiency virus-infected patients: three cases of renal failure, Fanconi syndrome, and nephrogenic diabetes insipidus. *Clin Infect Dis* 2003; **36**: 1070-1073 [PMID: 12684922]
93 **Pol S**, Lampertico P. First-line treatment of chronic hepatitis B with entecavir or tenofovir in 'real-life' settings: from clinical trials to clinical practice. *J Viral Hepat* 2012; **19**: 377-386 [PMID: 22571899 DOI: 10.1111/j.1365-2893.2012.01602.x]
94 **Gish RG**, Clark MD, Kane SD, Shaw RE, Mangahas MF, Baqai S. Similar risk of renal events among patients treated with tenofovir or entecavir for chronic hepatitis B. *Clin Gastroenterol Hepatol* 2012; **10**: 941-946; quiz e68 [PMID: 22507876 DOI: 10.1016/j.cgh.2012.04.008]
95 **Kim JH**, Jung SW, Byun SS, Shin JW, Park BR, Kim MH, Kim CJ, Park NH. Efficacy and safety of tenofovir in nucleos(t)ide-naïve patients with genotype C chronic hepatitis B in real-life practice. *Int J Clin Pharm* 2015; **37**: 1228-1234 [PMID: 26364195 DOI: 10.1007/s11096-015-0193-1]
96 **Lok AS**. Drug therapy: tenofovir. *Hepatology* 2010; **52**: 743-747 [PMID: 20597070 DOI: 10.1002/hep.23788]
97 **Daudé M**, Rostaing L, Sauné K, Lavayssière L, Basse G, Esposito L, Guitard J, Izopet J, Alric L, Kamar N. Tenofovir therapy in hepatitis B virus-positive solid-organ transplant recipients. *Transplantation* 2011; **91**: 916-920 [PMID: 21325995 DOI: 10.1097/TP.0b013e3182100f59]
98 **Tsai MC**, Chen CH, Hung CH, Lee CM, Chiu KW, Wang JH, Lu SN, Tseng PL, Chang KC, Yen YH, Hu TH. A comparison of efficacy and safety of 2-year telbivudine and entecavir treatment in patients with chronic hepatitis B: a match-control study. *Clin Microbiol Infect* 2014; **20**: O90-O100 [PMID: 23659493 DOI: 10.1111/1469-0691.12220]
99 **Ridruejo E**. Antiviral treatment for chronic hepatitis B in renal transplant patients. *World J Hepatol* 2015; **7**: 189-203 [PMID: 25729474 DOI: 10.4254/wjh.v7.i2.189]
100 **Koklu S**, Gulsen MT, Tuna Y, Koklu H, Yuksel O, Demir M, Guner R, Dogan Z, Kucukazman M, Poyrazoglu OK, Biyik M, Ozturk NA, Aydogan T, Coban S, Kocaman O, Sapmaz F, Gokturk SH, Karaca C, Demirezer A, Tanoglu A, Yildirim B, Altinbas A, Atak BM, Cosar AM, Alkan E. Differences in nephrotoxicity risk and renal effects among anti-viral therapies against hepatitis B. *Aliment Pharmacol Ther* 2015; **41**: 310-319 [PMID: 25982037 DOI: 10.1111/apt.13036]
101 **Levitsky J**, Doucette K; AST Infectious Diseases Community of Practice. Viral hepatitis in solid organ transplantation. *Am J Transplant* 2013; **13** Suppl 4: 147-168 [PMID: 23465008 DOI: 10.1111/ajt.12108]
102 **Gane EJ**, Deray G, Liaw YF, Lim SG, Lai CL, Rasenack J, Wang Y, Papatheodoridis G, Di Bisceglie A, Buti M, Samuel D, Uddin A, Bosset S, Trylesinski A. Telbivudine improves renal function in patients with chronic hepatitis B. *Gastroenterology* 2014; **146**: 138-146.e5 [PMID: 24067879 DOI: 10.1053/j.gastro.2013.09.031]
103 **Lin CL**, Chien RN, Yeh C, Hsu CW, Chang ML, Chen YC, Yeh CT. Significant renoprotective effect of telbivudine during preemptive antiviral therapy in advanced liver cancer patients receiving cisplatin-based chemotherapy: a case-control study. *Scand J Gastroenterol* 2014; **49**: 1456-1464 [PMID: 25283499 DOI: 10.3109/00365521.2014.962604]
104 **Pipili C**, Cholongitas E, Papatheodoridis G. Review article: nucleos(t)ide analogues in patients with chronic hepatitis B virus infection and chronic kidney disease. *Aliment Pharmacol Ther* 2014; **39**: 35-46 [PMID: 24299322 DOI: 10.1111/apt.12538]
105 **Wong F**, Pai R, Van Schalkwyk J, Yoshida EM. Hepatitis B in pregnancy: a concise review of neonatal vertical transmission and antiviral prophylaxis. *Ann Hepatol* 2014; **13**: 187-195 [PMID: 24552860]
106 **Yi P**, Chen R, Huang Y, Zhou RR, Fan XG. Management of mother-to-child transmission of hepatitis B virus: Propositions and challenges. *J Clin Virol* 2016; **77**: 32-39 [PMID: 26895227 DOI: 10.1016/j.jcv.2016.02.003]
107 **FDA Pregnancy Categories**. [Updated Mar 30th, 2016]. [Access date: Apr 24th, 2016]. Available from: http://www.drugs.com/pregnancy-categories.html
108 **Yu M**, Jiang Q, Ji Y, Jiang H, Wu K, Ju L, Tang X, Wu M. The efficacy and safety of antiviral therapy with lamivudine to stop the vertical transmission of hepatitis B virus. *Eur J Clin Microbiol Infect Dis* 2012; **31**: 2211-2218 [PMID: 22314409]
109 **Xu WM**, Cui YT, Wang L, Yang H, Liang ZQ, Li XM, Zhang SL, Qiao FY, Campbell F, Chang CN, Gardner S, Atkins M. Lamivudine in late pregnancy to prevent perinatal transmission of hepatitis B virus infection: a multicentre, randomized, double-blind, placebo-controlled study. *J Viral Hepat* 2009; **16**: 94-103 [PMID: 19175878 DOI: 10.1111/j.1365-2893.2008.01056.x]
110 **Antiretroviral Pregnancy Registry [Internet]**. WHO. [Updated 2015 Dec 17]. [Access date: 20.03.2016]. Available from: URL: http://www.apregistry.com/InterimReport.aspx
111 **Celen MK**, Mert D, Ay M, Dal T, Kaya S, Yildirim N, Gulsun S, Barcin T, Kalkanli S, Dal MS, Ayaz C. Efficacy and safety of tenofovir disoproxil fumarate in pregnancy for the prevention of vertical transmission of HBV infection. *World J Gastroenterol*

2013; **19**: 9377-9382 [PMID: 24409065 DOI: 10.3748/wjg.v19.i48.9377]

112 **Greenup AJ**, Tan PK, Nguyen V, Glass A, Davison S, Chatterjee U, Holdaway S, Samarasinghe D, Jackson K, Locarnini SA, Levy MT. Efficacy and safety of tenofovir disoproxil fumarate in pregnancy to prevent perinatal transmission of hepatitis B virus. *J Hepatol* 2014; **61**: 502-507 [PMID: 24801414 DOI: 10.1016/j.jhep.2014.04.038]

113 **Hu YH**, Liu M, Yi W, Cao YJ, Cai HD. Tenofovir rescue therapy in pregnant females with chronic hepatitis B. *World J Gastroenterol* 2015; **21**: 2504-2509 [PMID: 25741161 DOI: 10.3748/wjg.v21.i8.2504]

114 **Mirochnick M**, Thomas T, Capparelli E, Zeh C, Holland D, Masaba R, Odhiambo P, Fowler MG, Weidle PJ, Thigpen MC. Antiretroviral concentrations in breast-feeding infants of mothers receiving highly active antiretroviral therapy. *Antimicrob Agents Chemother* 2009; **53**: 1170-1176 [PMID: 19114673 DOI: 10.1128/AAC.01117-08]

P- Reviewer: El-Bendary MM, Zhao YL **S- Editor**: Song XX
L- Editor: Filipodia **E- Editor**: Li D

WJH
World Journal of Hepatology

Submit a Manuscript: http://www.wjgnet.com/esps/
DOI: 10.4254/wjh.v9.i5.242

World J Hepatol 2017 February 18; 9(5): 242-251
ISSN 1948-5182 (online)

REVIEW

Role of surgical resection for non-colorectal non-neuroendocrine liver metastases

Nobuyuki Takemura, Akio Saiura

Nobuyuki Takemura, Department of Gastroenterological Surgery, JR Tokyo General Hospital, Tokyo 151-8528, Japan

Nobuyuki Takemura, Akio Saiura, Department of Gastroenterological Surgery, Cancer Institute Ariake Hospital, Japanese Foundation for Cancer Research, Tokyo 151-8528, Japan

Author contributions: Takemura N analyzed the literatures and wrote the manuscript; Saiura A reviewed and edited the manuscript.

Conflict-of-interest statement: The authors have no conflicts of interest to declare in relation to the contents of this review.

Manuscript source: Invited manuscript

Correspondence to: Nobuyuki Takemura, MD, Department of Gastroenterological Surgery, JR Tokyo General Hospital, 2-1-3, Yoyogi, Shibuya-ku, Tokyo 151-8528, Japan. takemuranobu-tky@umin.ac.jp
Telephone: +81-3-33202200
Fax: +81-3-33707477

Received: August 30, 2016
Peer-review started: September 1, 2016
First decision: September 29, 2016
Revised: October 29, 2016
Accepted: December 7, 2016
Article in press: December 9, 2016
Published online: February 18, 2017

Abstract

It is widely accepted that the indications for hepatectomy in colorectal cancer liver metastases and liver metastases of neuro-endocrine tumors result in relatively better prognoses, whereas, the indications and prognoses of hepatectomy for non-colorectal non-neuroendocrine liver metastases (NCNNLM) remain controversial owing to the limited number of cases and the heterogeneity of the primary diseases. There have been many publications on NCNNLM; however, its background heterogeneity makes it difficult to reach a specific conclusion. This heterogeneous disease group should be discussed in the order from its general to specific aspect. The present review paper describes the general prognosis and risk factors associated with NCNNLM while specifically focusing on the liver metastases of each primary disease. A multidisciplinary approach that takes into consideration appropriate timing for hepatectomy combined with chemotherapy may prolong survival and/or contribute to the improvement of the quality of life while giving respite from systemic chemotherapy.

Key words: Non-colorectal non-neuroendocrine liver metastasis; Metastatic liver tumor; Hepatectomy; Gastric cancer liver metastasis; Gastrointestinal stromal tumor liver metastasis; Breast cancer liver metastasis; Melanoma liver metastasis; Sarcoma liver metastasis; Renal cell carcinoma liver metastasis; Ovarian cancer liver metastasis

Core tip: Previous studies reported that the results of hepatectomy for non-colorectal, non-neuroendocrine liver metastasis (NCNNLM) showed an acceptable prognosis in the heterogeneous disease group. However, considering the indication of hepatectomy for NCNNLM, it is important to define the features of each primary disease. The present review paper describes the general prognosis and risk factors associated with NCNNLM, specifically focuses on liver metastasis associated with each primary disease. A multidisciplinary approach that takes appropriate timing for hepatectomy combined with chemotherapy into consideration may prolong survival and/or contribute to the improvement of the quality of life, while taking time off from systemic chemotherapy.

Takemura N, Saiura A. Role of surgical resection for non-colorectal non-neuroendocrine liver metastases. *World J Hepatol* 2017; 9(5): 242-251 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i5/242.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i5.242

INTRODUCTION

Metastatic disease from solid organ tumors occurs frequently in the liver. Presently, surgical resection has been widely accepted as a treatment for colorectal cancer liver metastases[1,2] and liver metastases of neuro-endocrine tumors[3,4], providing a relatively better prognosis, whereas, the indications and prognosis of hepatectomy for non-colorectal non-neuroendocrine liver metastases (NCNNLM) remain controversial owing to the rarity of the disease. The biological behavior of NCNNLM varies depending on its primary origin. Discussion of this heterogeneous disease group should be performed in the order from its general to specific aspects. To date, no prospective randomized study has been conducted in this limited field; therefore, in this report we provide a general review of large cohort retrospective studies on hepatectomy for NCNNLM and a more specific review on hepatectomy for liver metastases from different primaries.

LITERATURE AND RESEARCH

In this report, we reviewed the literature reporting NCNNLM in a large number of patients and their specific primaries. More precisely, we reviewed articles in the English literature that included ⩾ 100 cases with NCNNLM and relatively large case series for the specific primary (for liver metastases from gastric cancer, breast cancer, and melanoma, reports that included ⩾ 40 cases were reviewed because of the limited availability of cases in many studies). Using the results reported in the selected literature, the survival outcomes and statistically significant risk factors that impacted survival by multivariate analysis (univariate analysis for some report) were evaluated.

Prognosis and risk factors after hepatectomy for NCNNLM

Along with increased evidence of prolonged survival by hepatectomy in patients with colorectal and neuro-endocrine liver metastases, Schwartz *et al*[5] initially categorized NCNNLM and reviewed the literatures in 1995, followed by the analysis of prognosis in a large cohort study by Harrison *et al*[6] in 1997. Many validation studies were performed in other patient cohorts that are summarized in Table 1[7-16]. In the present report, we reviewed the 10 largest studies, each with ⩾ 100 patients who underwent hepatectomy for NCNNLM. In this cohort, the 3- and 5-year overall survival rates were reported as 34%-57% and 19%-42%, respectively, with median survival times of 23-49 mo. The 3- and 5-year disease-free survival rates were 21%-37% and 18%-29%, respectively, with median disease-free survival times of 10-21 mo. The postoperative mortality and morbidity rates were reported 0%-5% and 18%-33%, respectively. In these cohort studies, the reported negative risk factors for survival were the margin status in six studies[8-11,15,16]; primary tumor type in four[8,10,11,15]; shorter disease-free interval between primary tumor resection and hepatectomy[8,10,15] and extrahepatic disease[10,12,16] in three; postoperative complications[14,16], larger hepatic metastasis in diameter[12,13], and squamous cell histology[10,15] in two; and age[10], major hepatectomy[10], minor hepatectomy[15], synchronous metastasis[11], lymphovascular invasion[13], stromal tumor histology[15] and > 3 liver metastases[16] in one (Table 1). Negative risk factors for recurrence were extrahepatic disease[12,16] in two studies; and primary tumor[8], disease-free interval[8], larger hepatic metastasis in diameter[12], blood transfusion[14], preoperative chemotherapy[14], > 3 liver metastases[16], and residual tumor[16] in one. Patients with liver metastases from breast cancer showed significantly better survival in three studies[10,11,15], whereas those with liver metastases from genitourinary tumor liver showed better survival in one[11], and patients with liver metastases from melanoma showed poorer survival compared to other primaries in two studies[10,15] (Table 2).

As previously mentioned, the type of primary origin was one of the greatest predictors of survival in patients with this heterogeneous disease. Among the 10 largest studies, the most dominant primary origin was the breast[7,10,13,15] and genitourinary[8,11,12,16] in four studies and gastrointestinal tract in two[9,14]. Elias *et al*[7] and Yedibela *et al*[9] commented that the resection of liver metastases from gastrointestinal adenocarcinoma correlated with a poor prognosis; however, a more recent report by Takemura *et al*[14] showed acceptable prognosis after resection of liver metastases from gastrointestinal carcinoma in their largest cohort with a median survival time of 33.5 mo after hepatectomy. As Yedibela *et al*[9] and Groeschl *et al*[13] reported that in the more recent years, patients undergoing hepatectomy for NCNNLM appeared to have longer survival compared to previous years, advances in chemotherapy regimens might contribute to prolong survival after the resection of NCNNLM. Adam *et al*[10] developed a risk model based on their results of multivariate prognostic factor analysis, which was validated by Lendoire *et al*[11]. Their risk model can efficiently stratify the patients into groups; however, the prognosis of each group differed between the two studies depending on the heterogeneous backgrounds of the patient. To facilitate discussion, the prognosis of each primary disease after hepatectomy for NCNNLM has been discussed separately in following section.

Table 1 Summary of studies each of which included ⩾ 100 patients who underwent hepatectomy for non-colorectal non-neuroendocrine liver metastases (overall survival)

Ref.	Year	Period	No. of patients	Primary tumor (GI/breast/GU/ melanoma/sarcoma/others)	MST (mo)	3-ysr (%)	5-ysr (%)	Factors associated with worse overall survival
Elias *et al*[7]	1998	1984-1996	120[1]	(22/35/31/10/13/9)	NR	NR	36[2]	NR
Yedibela *et al*[9]	2005	1978-2001	150[1]	(50/24/11/5/15/45)	23[2]	NR	26[2]	Margin status (R1,2)
Weitz *et al*[8]	2005	1981-2002	141	(12/29/50/17/0/33)	42	57	NR	Primary tumor type, disease-free interval ⩽ 24 mo, margin status (R1,2)
Adam *et al*[10]	2006	1983-2004	1452	(314/460/332/148/0/198)	35	49	36	Age, primary tumor (ocular melanoma, non-breast), squamous tumor, disease-free interval, extrahepatic disease, major hepatectomy, margin status (R1,2)
Lendoire *et al*[11]	2007	1989-2006	106	(7/19/40/6/23/11)	27	34	19	Primary tumor (non-breast, non-GU), synchronous metastasis, margin status (R1,2)
O'Rourke *et al*[12]	2008	1986-2006	102	(27/11/31/20/3/10)	42	56	39	Diameter of liver metastasis > 5 cm, extrahepatic nodal disease
Groeschl *et al*[13]	2012	1990-2009	420	(13/15/92/31/98/71)	49	50	31	Diameter of liver metastasis ⩾ 5 cm, lymphovascular invasion
Takemura *et al*[14]	2013	1993-2009	145	(91/30/12/1/8/3)	42	55	41	Postoperative complication
Hoffmann *et al*[15]	2015	2001-2012	150	(30/42/33/15/9/21)	46	NR	42	Primary tumor (melanoma, non-breast), interval < 24 mo, squamous tumor, non-stromal tumor, minor hepatectomy, margin (R2)
Schiergens *et al*[16]	2016	2003-2013	167	(43/16/61/8/25/14)	35	49	NR	> 3 liver metastases, extrahepatic disease, residual tumor (R1,2), major complications

[1]Patients with neuroendocrine tumors were excluded; [2]Results including neuroendocrine tumors. GI: Gastrointesti; GU: Genitourinary; MST: Median survival time; ysr: Year survival rate; NR: Not reported.

Table 2 Summary of studies each of which included ⩾ 100 patients who underwent hepatectomy for non-colorectal non-neuroendocrine liver metastases (disease-free survival)

Ref.	Year	No. of patients	MDFST (mo)	3-ydfsr (%)	5-ydfsr (%)	Factors associated with worse disease-free survival
Elias *et al*[7]	1998	120[1]	NR	NR	28[2]	NR
Yedibela *et al*[9]	2005	150[1]	NR	NR	NR	NR
Weitz *et al*[8]	2005	141	17	30	NR	Primary tumor, diseas-free interval ⩽ 24 mo
Adam *et al*[10]	2006	1452	13	27	21	NR
Lendoire *et al*[11]	2007	106	NR	NR	NR	NR
O'Rourke *et al*[12]	2008	102	18	37	27	Diameter of liver metastasis > 5 cm, extrahepatic nodal disease
Groeschl *et al*[13]	2012	420	NR	NR	NR	NR
Takemura *et al*[14]	2013	145	10	21	18	Blood transfusuion, preoperative chemotherapy
Hoffmann *et al*[15]	2015	150	21	36	29	NR
Schiergens *et al*[16]	2016	167	15	NR	NR	> 3 liver metastases, extrahepatic disease, residual tumor (R1,2)

[1]Patients with neuroendocrine tumors were excluded; [2]Results including neuroendocrine tumors. MDFST: Median disease-free survival time; ydfsr: Year disease-free survival ratio; NR: Not reported.

LIVER METASTASES FROM GASTROINTESTINAL PRIMARY TUMORS

Gastric cancer liver metastases

In the present report, we reviewed the largest 8 studies, each with ⩾ 40 patients who underwent hepatectomy for liver metastases from gastric cancer. In this series, the 3- and 5-year overall survival rates were reported as 14%-51% and 9%-42%, respectively, with median survival times of 12-41 mo (Table 3)[10,17-23]. Among these studies, the negative risk factors for survival were multiple liver metastases in three studies[18,20,23]; larger hepatic metastasis in diameter[19,21] and serosal invasion of primary gastric cancer[19,21] in two; and synchronous hepatic metastases[17], > 3 liver metastases[21] and > 2 positive regional lymph node metastases of primary gastric cancer[23] in one (Table 3). The results of hepatectomy for liver metastasis from gastric cancer are influenced by the statuses of both the primary cancer and liver metastasis. The recent meta-analysis of gastric cancer liver metastases revealed that the surgical resection of liver metastases from gastric cancer was associated with a significantly improved survival and among the patients who underwent surgical resection, patients with solitary hepatic metastasis demonstrated a significantly prolonged survival compared to patients with

Table 3 Summary of studies each of which included ≥ 40 patients who underwent hepatectomy for liver metastasis from gastric cancer

Ref.	Year	Period	No. of patients	MST (mo)	3-ysr (%)	5-ysr (%)	Factors associated with worse overall survival
Ambiru *et al*[17]	2001	1975-1999	40	12	NR	18	Synchronous metastasis
Adam *et al*[10]1	2006	1983-2004	64	15	NR	27	NR
Cheon *et al*[18]	2008	1995-2005	41	18	32	21	Multiple liver metastases
Takemura *et al*[19]	2012	1993-2011	64	34	50	37	Serosal invasion of primary gastric cancer, maximum hepatic metastasis diameter > 5 cm
Aizawa *et al*[20]	2014	1997-2010	53	27	NR	18	Multiple liver metastases
Kinoshita *et al*[21]	2014	1990-2010	256	31	42	31	Serosal invasion of primary gastric cancer, > 3 liver metastases, maximum hepatic metastasis diameter > 5 cm
Tiberio *et al*[22]	2015	1997-2011	53	13	14	9	NR2
Oki *et al*[23]	2015	2000-2010	69	41	51	42	Multiple liver metastases, > 2 positive regional lymph node metastases of primary gastric cancer

1As a part of the report of on-colorectal non-neuroendocrine liver metastases; 2Only risk factors including palliative patients were reported. MST: Median survival time; ysr: Year survival rate; NR: Not reported.

Table 4 Summary of studies with relatively large cohort of patients who underwent hepatectomy for liver metastasis from gastrointestinal stromal tumors

Ref.	Year	Period	No. of patients underwent hepatectomy	MST (mo)	3-ysr (%)	5-ysr (%)	3-yPFS (%)	No. of patients with TKI	Factors associated with worse overall survival
DeMatteo *et al*[26]	2001	1982-2000	34[1]	39[1]	50[1]	30[1]	45[1]	NR	Interval from primary tumor diagnosis ≤ 24 mo[2]
Nunobe *et al*[27]	2005	1984-2003	18	36	64	34	NR	3 (17%)	NR
Xia *et al*[28]	2010	2005	19	33 (mean)	90	NR	NR	19 (100%)	Non-surgical therapy[2]
Turley *et al*[29]	2012	1995-2010	39	Not reached at 5 yr	68	NR	NR	27 (73%)[3]	Non-TKI therapy, extrahepatic disease
Bauer *et al*[30]	2014	Until 2011	104	96	NR	NR	NR	> 84%	Male[4], R2 resection[4], progression disease to TKI at the time of surgery[4], extrahepatic disease[4]
Du *et al*[31]	2014	NR	19	Not reached	NR	NR	88 (2-yr)	19 (100%)	Non-surgical therapy[2]
Seesing *et al*[32]	2016	1999-2014	48	90	80	76	67	42 (88%)	Margin status (R1,2)

1Including gastrointestinal sarcoma; 2Copmarison to the non-operation group; 3Excluding two patients lost to follow-up; 4Results including resections of extrahepatic metastasis. GIST: Gastrointestinal stromal tumor; MST: Median survival time; ysr: Year survival rate; PFS: Progression-free survival; TKI: Tyrosine kinase inhibitor; NR: Not reported.

multiple hepatic metastases[24]. Compared to colorectal liver metastasis, reports on aggressive repeat hepatectomy have been highly limited[25], which might be owing to the frequent occurrence of extrahepatic recurrence such as peritoneal seeding and lymph node recurrence. However, advancements in effective chemotherapy regimens can expand not only the prognosis but also the surgical indications for hepatectomy in patients with liver metastasis from gastric cancer and colorectal live metastases alike.

Gastrointestinal stromal tumors liver metastases

The 7 largest studies on the hepatectomy for liver metastases from gastrointestinal stromal tumors (GIST) reported 50%-90% and 30%-76% overall 3- and 5-year survival rates, respectively, with median survival times of 33-96 mo (Table 4)[26-32]. Non-surgical therapy[28,31], positive resection margin[30,32], and extrahepatic disease[29,30] in two studies each and a disease free interval ≤ 24 mo[26], absence of tyrosine kinase inhibitor (TKI) therapy[29], male patients[30] and progression disease to TKI therapy at the time of surgery[30] were the factors associated with worse survival (Table 4). Different from other NCNNLMs, the emergence of TKI dramatically changed the treatment and prognoses of patients with advanced GIST. The role of surgical resection in the treatment of metastatic GIST had remained unclear in the initial era of treatment with TKI[33]; however, recent reports showed evidence that surgical resection combined with TKI offered better prognosis than TKI monotherapy[29,31,32]. As Bauer *et al*[30] reported progression disease to TKI therapy at the time of surgery, an urgent issue to debate is the appropriate duration of preoperative therapy to minimize the risk of acquiring secondary mutations responsible for TKI resistance[26,29].

Other gastro-intestinal primary tumor liver metastases

Pertaining to reports of liver resection for other gastro-intestinal primary liver metastases that rarely indicated hepatectomy, esophagus and pancreas cancer liver metastasis showed dismal prognosis with a median overall survival time of 7-20 mo[10,16,34,35]. In the mean-

Table 5 Summary of studies with relatively large cohort of patients who underwent hepatectomy for liver metastases from gastrointestinal primaries other than gastric cancer and gastrointestinal stromal tumors

Disease	Ref.	Year	Period	No. of patients	MST (mo)	3-ysr (%)	5-ysr (%)	Factors associated with worse overall survival
Peri-ampullary	De Jong *et al*[34]	2010	1993-2009	40	17 [23 (intestinal), 13 (pancreaticobiliary)]	18	NR	Intestinal type (ampullary or duodenal) tumors
Ampullary	Adam *et al*[10]1	2006	1983-2004	15	38	NR	46	NR
Small bowel	Adam *et al*[10]1	2006	1983-2004	28	58	NR	49	NR
Pancreas	Adam *et al*[10]1	2006	1983-2004	40	20	NR	25	NR
	Schiergens *et al*[16]1	2016	2003-2013	19	7	17	NR	NR
Esophagous	Adam *et al*[10]1	2006	1983-2004	20	16	32	NR	NR
	Ichida *et al*[35]	2013	2003-2005	5	13	NR	NR	NR

1As a part of the report of on-colorectal non-neuroendocrine liver metastases. MST: Median survival time; ysr: Year survival rate; NR: Not reported.

Table 6 Summary of studies with ≥ 40 patients who underwent hepatectomy for liver metastasis from breast cancer

Ref.	Year	Period	No. of patients	MST (mo)	3-ysr (%)	5-ysr (%)	MDFS (mo)	Factors associated with worse overall survival
Pocard *et al*[36]	2000	1988-1997	52	42	49	NR	NR	Disease free interval ≤ 48 mo (univariate)
Elias *et al*[37]	2003	1986-2000	54	34	50	34	NR	Hormone receptor-negative
Adam *et al*[38]	2006	1984-2004	85	32	NR	37	20	Poor response to preoperative chemotherapy, R2, no repeat hepatectomy
Adam *et al*[10]1	2006	1983-2004	454	45	NR	41	NR	NR
Hoffman *et al*[39]	2010	1999-2008	41	58	68	48	34	Positive resection margin, disease-free interval < 24 mo
Abbott *et al*[40]	2012	1997-2010	86	57	NR	44	14	ER-negative, disease progression before hepatectomy
Groeschl *et al*[13]1	2012	1990-2009	115	52	52	27	22	NR
Mariani *et al*[41]	2013	1988-2007	51	91	NR	NR	NR	Non-hepatectomy3, bone metastasis4
Hoffmann *et al*[15]1	2015	2001-2012	42	63	NR	53	NR	NR
Sadot *et al*[42]	2016	1991-2014	692	502	NR	382	29	Lymph node metastasis in the primary tumor, absence of trastuzumab therapy, multiple liver metastases

1As a part of the report of on-colorectal non-neuroendocrine liver metastases; 2Including 18 patients who underwent percutaneous ablation therapy; 3Comparison to the non-operation group; 4Comparison including patients without hepatectomy. MST: Median survival time; ysr: Year survival rate; NR: Not reported.

while, intestinal type primary tumors such as duodenal, ampullary and small intestinal cancer showed relatively better prognosis with median survival times of 23-58 mo[10,34] (Table 5).

LIVER METASTASES FROM BREAST CANCER

The largest 10 studies, each with ≥ 40 patients who underwent hepatectomy for liver metastases from breast cancer were reviewed. In this series, the 3- and 5-year overall survivals rates were 49%-68% and 27%-53%, respectively, with median survival times of 41-115 mo (Table 6)[10,13,15,36-42]. The negative prognostic predictive factors were short disease-free interval[36,39], negative expression of hormone receptors[37,40], poor response to systemic chemotherapy before surgery[38,40], and positive hepatic resection margin[38,39] in two studies; and the absence of repeat hepatectomy[38], non-hepatectomy[41], bone metastasis[41], lymph node metastasis in the primary tumor[42], absence of trastuzumab therapy[42], and multiple liver metastases[42] in one (Table 6). Some prognostic factors of liver metastases from breast cancer are unique and different from other NCNNLMs, which could indicate that the presence of hormone receptors and HER2 overexpression requires the use of chemotherapy and/or hormone therapy and influences patient survival. Neuman *et al*[43] suggested that the impact of local control for liver metastases from breast cancer was greatest in the presence of effective targeted therapy. Similar to other NCNNLMs, surgical resection before progression of disease even with chemotherapy might result in better outcomes of selected patients with liver metastases from breast cancer[40]. As Sadot *et al*[42] advocated in their study, hepatic resection for liver metastases from breast cancer might not confer a survival advantages; however, might allow time off from systemic chemotherapy.

LIVER METASTASES FROM MELANOMA

The largest four studies, each with ≥ 40 patients who underwent liver resection for liver metastases from melanoma, reported an overall 5-year survival rate of approximately 7%-20% with a median survival time of 14-28 mo (Table 7)[10,44-46]. Short disease-free interval from the diagnosis of primary tumor[45], positive resection

Table 7 Summary of studies with ≥ 40 patients who underwent hepatectomy for liver metastasis from melanoma

Ref.	Year	Period	No. of patients	Ocular/ cutaneous	MST (mo) (ocular/ cutaneous)	3-ysr (%)	5-ysr (%)	Factors associated with worse overall survival
Adam *et al*[10]1	2006	1983-2004	148	104/44	19/27	NR	21 (ocular)/22 (cutaneous)	NR
Pawlik *et al*[44]	2006	1988-2004	40	16/24	28 [29 (ocular)/24 (cutaneous)]	62 (ocular)/48 (cutaneous) (2-yr)	11 (21 (ocular)/0 (cutaneous))	Cutaneous melanoma, no preoperative chemotherapy (in cutaneous melanoma) (univariable)
Mariani *et al*[45]	2009	1991-2007	255 (R2 = 157)	255/0	14 (27 mo after R0 resection)	NR	7	Interval from primary tumor diagnosis ≤ 24 mo, R1 and R2, number of the metastases > 4, miliary disease
Mariani *et al*[46]	2016	2000-2013	70 (inclding 13 concomitant with RFA)	70/0	27 (hepatectomy), 28 (+RFA)	NR	NR	NR

[1]As a part of the report of on-colorectal non-neuroendocrine liver metastases. MST: Median survival time; ysr: Year survival rate; NR: Not reported.

Table 8 Summary of studies with relatively large cohort of patients who underwent hepatectomy for liver metastasis from sarcoma

Ref.	Year	Period	No. of patients	MST (mo)	3-ysr (%)	5-ysr (%)	Factors associated with worse overall survival
Lang *et al*[48]	2000	1982-1996	26 (including 9 second, 2 third resection)	32 (R0 first resection), 21 (R1,2 resection)	NR	13	NR
DeMatteo *et al*[26]1	2001	1982-2000	56[1]	39[1]	50[1]	30[1]	Time to liver metastasis from the primary tumor diagnosis ≤ 24 mo
Pawlik *et al*[49]	2006	1996-2005	53 (35Hx, 18RF + Hx, and 13RF), (including 36 GISTs)	47[2]	65[2]	27[2]	Non-GIST
Marudanayagam *et al*[50]	2011	1997-2009	36[1] (including 5 GISTs)	24	48	32	Primaly leiomyosarcoma
Groeschl *et al*[13]3	2012	1990-2009	98	72	60	32	NR
Zhang *et al*[51]	2015	2000-2009	27	NR	NR	46	Interval from primary tumor diagnosis ≤ 24 mo, extrahepatic disease, positive margins

[1]Including some patients with GIST before 1993, GISTs were considered as leiomyosarcomas; [2]Including results of RF and patients with GIST; [3]As a part of the report of on-colorectal non-neuroendocrine liver metastases. GIST: Gastrointestinal stromal tumor; MST: Median survival time; ysr: Year survival rate; NR: Not reported; Hx: Hepatectomy; RF: Radiofrequency ablation.

margin[45], > 4 liver metastases[45], miliary disease of the primary melanoma[45], cutaneous melanoma[46], and no preoperative chemotherapy were the risk factors predicting poor patients survival (Table 7). The metastatic pathway of ocular and cutaneous melanomas is different. Ocular melanoma often spreads hematogenously to the liver because there are no lymphatics in the uveal tract. In contrast, cutaneous melanomas potentially spread to the lung, lymph node and soft tissue, and infrequently to the liver[47]. Liver metastases from ocular melanoma often recur within the liver, whereas cutaneous melanoma is more likely to develop extrahepatic recurrence[44]. Surgical resection should be performed concomitantly with system in chemotherapy as part of a multidisciplinary approach because recurrent disease frequently develops after hepatectomy.

LIVER METASTASES FROM SARCOMA

The six largest studies on the resection of liver metastases from sarcoma reported 50%-65% and 13%-46% overall 3- and 5-year survival rates, respectively, with median survival times of 24-72 mo (Table 8)[13,26,48-51]. Negative risk factors for overall survival in this cohort were a time of < 24 mo from the diagnosis of primary tumor to the time of liver metastasis[26,51], non-GIST[49], leiomyosarcoma[50], extrahepatic disease[51], and positive resection margins[51] (Table 8). These studies included some GIST patients particularly in the early study periods because GIST had been considered as leiomyosarcoma before around 1993. Repeat hepatic resection was reported in four studies. Lang *et al*[48] reported 9 second and 2 third cases of hepatectomy for intrahepatic recurrent sarcoma. Less sensitivity to chemotherapy might prompt the surgeon to conduct a repeat hepatectomy with R0 resection, resulting in a favorable outcome[48].

LIVER METASTASES FROM GENITOURINARY TUMORS

Genitourinary tumors mainly comprise renal cell carcinoma, gynecological carcinoma most commonly with ovarian cancer, and testicular cancer. In the present report, we have reviewed 6 studies pertaining to liver metastases from the renal cell carcinoma which reported

Table 9 Summary of studies with relatively large cohort of the patients who underwent hepatectomy for liver metastasis from genitourinary primary tumor

Disease	Ref.	Year	Period	No. of patients	MST (mo)	3-ysr (%)	5-ysr (%)	Factors associated with worse overall survival
Renal cell carcinoma	Adam *et al*[10]1	2006	1983-2004	85	36	NR	38	NR
	Thelen *et al*[52]	2007	1988-2006	31	48	54	39	Resection margin (R1,2)
	Staehler *et al*[53]	2010	1995-2006	68	142	NR	62	High-grade primary renal cell carcinoma, performance status ≥ 1, lymph node status
	Ruys *et al*[54]	2011	1990-2008	29	33	47	43	Synchronous metastases, R1,2 resection margin (univariate)
	Hatzaras *et al*[55]	2012	1994-2011	43	Not reached	62	NR	Disease-free interval ≤ 12 mo, exrahepatic disease (univariate)
	Schiergens *et al*[16]1	2016	2003-2013	28	50	68	NR	NR
Gyneclogic primary	Kamel *et al*[56]	2011	1990-2010	52	53	57	41	NR
Ovarian cancer	Merideth *et al*[57]	2003	1976-1999	26[2]	26	NR	NR	Interval from the primary diagnosis < 12 mo, residual disease > 1 cm (univariate)
	Adam *et al*[10]1	2006	1983-2004	65	98	NR	50	NR
	Lim *et al*[58]	2009	2001-2008	14[2]	Not reached	NR	51	Hematogeneous liver metastasis < hepatic parenchymal metastasis from peritoneal seeding[5]
	Neumann *et al*[59]	2012	1991-2007	41	42(R0 resection)	NR	NR	R1,2 resection, pre-operative ascites, bilobular liver metastasis
	Niu *et al*[60]	2012	2000-2011	60	39	NR	30	R1,2 resection
	Kolev *et al*[61]	2014	1988-2012	27[3]	56	NR	NR	Interval from the primary surgery ≤ 24 mo, residual disease ≥ 1 cm
	Bacalbasa *et al*[62]	2015	2002-2014	31[2,4]	16 (metastasis from seeding), 13 (hematogeneous)	NR	NR	No significant risk factor
	Schiergens *et al*[16]1	2016	2003-2013	24	33	43	NR	NR
Testicular cancer	Hahn *et al*[63]	1999	1974-1996	57	NR	97 (2-yr)	NR	NR
	Adam *et al*[10]1	2006	1983-2004	78	82	NR	51	NR

[1]As a part of the report of on-colorectal non-neuroendocrine liver metastases; [2]As a part of debulking surgery; [3]Hepatectomy as secondary cytoreduction; [4]Including 2nd (*n* = 15), 3rd (3) and 4th (2) cytoreduction operations; [5]Only risk factors that included patients undergoing palliative treatment were reported. MST: Median survival time; ysr: Year survival rate; NR: Not reported.

overall 3- and 5-year survival rate of 54%-68% and 38%-62%, respectively, with median survival times of 33-142 mo (Table 9)[10,16,52-55]. The negative prognostic risk factors were the resection margin[52,54], high-grade tumor[53], poor performance status[53], lymph node metastasis[53], synchronous metastasis[54], short disease-free interval[55], and extra hepatic disease[55] (Table 9). Staehler *et al*[53] is the first to advocate a favorable prognosis for hepatectomy in patients who underwent resection of liver metastases from renal cell carcinoma over the prognosis of patients who refused to undergo hepatectomy for metastatic renal cell carcinoma, albeit the requirement for further systemic treatment.

The nine largest studies pertaining to gynecological primary cancers, particularly with ovarian cancer, reported 5-year overall survival rates of 30%-51% with median survival times of 26-98 mo (Table 9)[10,16,56-62]. Factors associated with worse survival were shorter interval from the diagnosis of primary disease to metastasis[56,61], residual tumor measuring > 1 cm[56,61], hematogenous liver metastasis[57], positive resection margins[59,60], pre-operative ascites[59], and bi-lobular hepatic metastasis[59] (Table 9). Owing to the unique features of ovarian cancer, hepatectomy was regarded as a part of cytoreductive surgery and concomitant chemotherapy, which has been accepted as the standard treatment for advanced ovarian cancer. In contrast to other NCNNLMs, the resection of liver metastases from the peritoneal seeding showed better prognosis than resection of hematogenous liver metastases[57].

Chemotherapy is highly effective in the treatment of testicular carcinoma; however, one-third of the patients either did not achieve complete responces or experienced relapses[63]. The limited studies involving treatment with sensitive chemotherapy and subsequent hepatectomy for testicular carcinoma have sufficiently demonstrated a favorable prognosis in patients who underwent this treatment regimen[63].

CONCLUSION

The clinical evidence accumulated with regards to NCNNLM has indicated the possibility of a chemotherapy-free period and a few studies have demonstrated a curing potential; however, almost all studies reviewed in the present report were conducted retrospectively in selected patients who underwent hepatic resection, which makes determining the absolute indications for hepatectomy in patients with NCNNLM challenging. Indications of hepatectomy for NCNNLM change according to the development of chemotherapy regimens. Strong and highly effective chemotherapy regimens might either expand the indications for hepatectomy or replace hepatectomy in this field. A multidisciplinary approach is required for the treatment of patients with diseases that are otherwise difficult to treat.

REFERENCES

1 **Rees M**, Tekkis PP, Welsh FK, O'Rourke T, John TG. Evaluation of long-term survival after hepatic resection for metastatic colorectal cancer: a multifactorial model of 929 patients. *Ann Surg* 2008; **247**: 125-135 [PMID: 18156932 DOI: 10.1097/SLA.0b013e31815aa2c2]

2 **de Jong MC**, Pulitano C, Ribero D, Strub J, Mentha G, Schulick RD, Choti MA, Aldrighetti L, Capussotti L, Pawlik TM. Rates and patterns of recurrence following curative intent surgery for colorectal liver metastasis: an international multi-institutional analysis of 1669 patients. *Ann Surg* 2009; **250**: 440-448 [PMID: 19730175 DOI: 10.1097/SLA.0b013e3181b4539b]

3 **Mayo SC**, de Jong MC, Pulitano C, Clary BM, Reddy SK, Gamblin TC, Celinksi SA, Kooby DA, Staley CA, Stokes JB, Chu CK, Ferrero A, Schulick RD, Choti MA, Mentha G, Strub J, Bauer TW, Adams RB, Aldrighetti L, Capussotti L, Pawlik TM. Surgical management of hepatic neuroendocrine tumor metastasis: results from an international multi-institutional analysis. *Ann Surg Oncol* 2010; **17**: 3129-3136 [PMID: 20585879 DOI: 10.1245/s10434-010-1154-5]

4 **Saxena A**, Chua TC, Sarkar A, Chu F, Liauw W, Zhao J, Morris DL. Progression and survival results after radical hepatic metastasectomy of indolent advanced neuroendocrine neoplasms (NENs) supports an aggressive surgical approach. *Surgery* 2011; **149**: 209-220 [PMID: 20674950 DOI: 10.1016/j.surg.2010.06.008]

5 **Schwartz SI**. Hepatic resection for noncolorectal nonneuroendocrine metastases. *World J Surg* 1995; **19**: 72-75 [PMID: 7740813 DOI: 10.1007/BF00316982]

6 **Harrison LE**, Brennan MF, Newman E, Fortner JG, Picardo A, Blumgart LH, Fong Y. Hepatic resection for noncolorectal, nonneuroendocrine metastases: a fifteen-year experience with ninety-six patients. *Surgery* 1997; **121**: 625-632 [PMID: 9186462 DOI: 10.1016/S0039-6060(97)90050-7]

7 **Elias D**, Cavalcanti de Albuquerque A, Eggenspieler P, Plaud B, Ducreux M, Spielmann M, Theodore C, Bonvalot S, Lasser P. Resection of liver metastases from a noncolorectal primary: indications and results based on 147 monocentric patients. *J Am Coll Surg* 1998; **187**: 487-493 [PMID: 9809564 DOI: 10.1016/S1072-7515(98)00225-7]

8 **Weitz J**, Blumgart LH, Fong Y, Jarnagin WR, D'Angelica M, Harrison LE, DeMatteo RP. Partial hepatectomy for metastases from noncolorectal, nonneuroendocrine carcinoma. *Ann Surg* 2005; **241**: 269-276 [PMID: 15650637 DOI: 10.1097/01.sla.0000150244.72285.ad]

9 **Yedibela S**, Gohl J, Graz V, Pfaffenberger MK, Merkel S, Hohenberger W, Meyer T. Changes in indication and results after resection of hepatic metastases from noncolorectal primary tumors: a single-institutional review. *Ann Surg Oncol* 2005; **12**: 778-785 [PMID: 16132374 DOI: 10.1245/ASO.2005.11.018]

10 **Adam R**, Chiche L, Aloia T, Elias D, Salmon R, Rivoire M, Jaeck D, Saric J, Le Treut YP, Belghiti J, Mantion G, Mentha G. Hepatic resection for noncolorectal nonendocrine liver metastases: analysis of 1,452 patients and development of a prognostic model. *Ann Surg* 2006; **244**: 524-535 [PMID: 16998361 DOI: 10.1097/01.sla.0000239036.46827.5f]

11 **Lendoire J**, Moro M, Andriani O, Grondona J, Gil O, Raffin G, Silva J, Bracco R, Podestá G, Valenzuela C, Imventarza O, Pekolj J, De Santibañes E. Liver resection for non-colorectal, non-neuroendocrine metastases: analysis of a multicenter study from Argentina. *HPB* (Oxford) 2007; **9**: 435-439 [PMID: 18345290 DOI: 10.1080/13651820701769701]

12 **O'Rourke TR**, Tekkis P, Yeung S, Fawcett J, Lynch S, Strong R, Wall D, John TG, Welsh F, Rees M. Long-term results of liver resection for non-colorectal, non-neuroendocrine metastases. *Ann Surg Oncol* 2008; **15**: 207-218 [PMID: 17963007 DOI: 10.1245/s10434-007-9649-4]

13 **Groeschl RT**, Nachmany I, Steel JL, Reddy SK, Glazer ES, de Jong MC, Pawlik TM, Geller DA, Tsung A, Marsh JW, Clary BM, Curley SA, Gamblin TC. Hepatectomy for noncolorectal non-neuroendocrine metastatic cancer: a multi-institutional analysis. *J Am Coll Surg* 2012; **214**: 769-777 [PMID: 22425166 DOI: 10.1016/j.jamcollsurg.2011.12.048]

14 **Takemura N**, Saiura A, Koga R, Arita J, Yoshioka R, Ono Y, Sano T, Yamamoto J, Kokudo N, Yamaguchi T. Long-term results of hepatic resection for non-colorectal, non-neuroendocrine liver metastasis. *Hepatogastroenterology* 2013; **60**: 1705-1712 [PMID: 23933784 DOI: 10.5754/hge13078]

15 **Hoffmann K**, Bulut S, Tekbas A, Hinz U, Büchler MW, Schemmer P. Is Hepatic Resection for Non-colorectal, Non-neuroendocrine Liver Metastases Justified? *Ann Surg Oncol* 2015; **22** Suppl 3: S1083-S1092 [PMID: 26242369 DOI: 10.1245/s10434-015-4775-x]

16 **Schiergens TS**, Lüning J, Renz BW, Thomas M, Pratschke S, Feng H, Lee SM, Engel J, Rentsch M, Guba M, Werner J, Thasler WE. Liver Resection for Non-colorectal Non-neuroendocrine Metastases: Where Do We Stand Today Compared to Colorectal Cancer? *J Gastrointest Surg* 2016; **20**: 1163-1172 [PMID: 26921025 DOI: 10.1007/s11605-016-3115-1]

17 **Ambiru S**, Miyazaki M, Ito H, Nakagawa K, Shimizu H, Yoshidome H, Shimizu Y, Nakajima N. Benefits and limits of hepatic resection for gastric metastases. *Am J Surg* 2001; **181**: 279-283 [PMID: 11376587 DOI: 10.1016/S0002-9610(01)00567-0]

18 **Cheon SH**, Rha SY, Jeung HC, Im CK, Kim SH, Kim HR, Ahn JB, Roh JK, Noh SH, Chung HC. Survival benefit of combined curative resection of the stomach (D2 resection) and liver in gastric cancer patients with liver metastases. *Ann Oncol* 2008; **19**: 1146-1153 [PMID: 18304963 DOI: 10.1093/annonc/mdn026]

19 **Takemura N**, Saiura A, Koga R, Arita J, Yoshioka R, Ono Y, Hiki N, Sano T, Yamamoto J, Kokudo N, Yamaguchi T. Long-term outcomes after surgical resection for gastric cancer liver metastasis: an analysis of 64 macroscopically complete resections. *Langenbecks Arch Surg* 2012; **397**: 951-957 [PMID: 22615045 DOI: 10.1007/s00423-012-0959-z]

20 **Aizawa M**, Nashimoto A, Yabusaki H, Nakagawa S, Matsuki A. Clinical benefit of surgical management for gastric cancer with synchronous liver metastasis. *Hepatogastroenterology* 2014; **61**: 1439-1445 [PMID: 25513107]

21 **Kinoshita T**, Kinoshita T, Saiura A, Esaki M, Sakamoto H, Yamanaka T. Multicentre analysis of long-term outcome after surgical resection for gastric cancer liver metastases. *Br J Surg* 2015; **102**: 102-107 [PMID: 25389030 DOI: 10.1002/bjs.9684]

22 **Tiberio GA**, Baiocchi GL, Morgagni P, Marrelli D, Marchet A, Cipollari C, Graziosi L, Ministrini S, Vittimberga G, Donini A, Nitti D, Roviello F, Coniglio A, de Manzoni G. Gastric cancer and synchronous hepatic metastases: is it possible to recognize candidates to R0 resection? *Ann Surg Oncol* 2015; **22**: 589-596 [PMID: 25190117 DOI: 10.1245/s10434-014-4018-6]

23 **Oki E**, Tokunaga S, Emi Y, Kusumoto T, Yamamoto M, Fukuzawa K, Takahashi I, Ishigami S, Tsuji A, Higashi H, Nakamura T, Saeki H, Shirabe K, Kakeji Y, Sakai K, Baba H, Nishimaki T, Natsugoe S, Maehara Y. Surgical treatment of liver metastasis of gastric cancer: a retrospective multicenter cohort study (KSCC1302). *Gastric Cancer* 2016; **19**: 968-976 [PMID: 26260876 DOI: 10.1007/s10120-015-0530-z]

24 **Markar SR**, Mikhail S, Malietzis G, Athanasiou T, Mariette C, Sasako M, Hanna GB. Influence of Surgical Resection of Hepatic Metastases From Gastric Adenocarcinoma on Long-term Survival: Systematic Review and Pooled Analysis. *Ann Surg* 2016; **263**: 1092-1101 [PMID: 26797324 DOI: 10.1097/SLA.0000000000001542]

25 **Takemura N**, Saiura A, Koga R, Yoshioka R, Yamamoto J, Kokudo N. Repeat hepatectomy for recurrent liver metastasis from gastric carcinoma. *World J Surg* 2013; **37**: 2664-2670 [PMID: 23963347 DOI: 10.1007/s00268-013-2190-7]

26 **DeMatteo RP**, Shah A, Fong Y, Jarnagin WR, Blumgart LH, Brennan MF. Results of hepatic resection for sarcoma metastatic to liver. *Ann Surg* 2001; **234**: 540-547; discussion 547-548 [PMID:

11573047 DOI: 10.1097/00000658-200110000-00013]
27 **Nunobe S**, Sano T, Shimada K, Sakamoto Y, Kosuge T. Surgery including liver resection for metastatic gastrointestinal stromal tumors or gastrointestinal leiomyosarcomas. *Jpn J Clin Oncol* 2005; **35**: 338-341 [PMID: 15928191 DOI: 10.1093/jjco/hyi091]
28 **Xia L**, Zhang MM, Ji L, Li X, Wu XT. Resection combined with imatinib therapy for liver metastases of gastrointestinal stromal tumors. *Surg Today* 2010; **40**: 936-942 [PMID: 20872196 DOI: 10.1007/s00595-009-4171-x]
29 **Turley RS**, Peng PD, Reddy SK, Barbas AS, Geller DA, Marsh JW, Tsung A, Pawlik TM, Clary BM. Hepatic resection for metastatic gastrointestinal stromal tumors in the tyrosine kinase inhibitor era. *Cancer* 2012; **118**: 3571-3578 [PMID: 22086856 DOI: 10.1002/cncr.26650]
30 **Bauer S**, Rutkowski P, Hohenberger P, Miceli R, Fumagalli E, Siedlecki JA, Nguyen BP, Kerst M, Fiore M, Nyckowski P, Hoiczyk M, Cats A, Casali PG, Treckmann J, van Coevorden F, Gronchi A. Long-term follow-up of patients with GIST undergoing metastasectomy in the era of imatinib -- analysis of prognostic factors (EORTC-STBSG collaborative study). *Eur J Surg Oncol* 2014; **40**: 412-419 [PMID: 24491288 DOI: 10.1016/j.ejso.2013.12.020]
31 **Du CY**, Zhou Y, Song C, Wang YP, Jie ZG, He YL, Liang XB, Cao H, Yan ZS, Shi YQ. Is there a role of surgery in patients with recurrent or metastatic gastrointestinal stromal tumours responding to imatinib: a prospective randomised trial in China. *Eur J Cancer* 2014; **50**: 1772-1778 [PMID: 24768330 DOI: 10.1016/j.ejca.2014.03.280]
32 **Seesing MF**, Tielen R, van Hillegersberg R, van Coevorden F, de Jong KP, Nagtegaal ID, Verhoef C, de Wilt JH. Resection of liver metastases in patients with gastrointestinal stromal tumors in the imatinib era: A nationwide retrospective study. *Eur J Surg Oncol* 2016; **42**: 1407-1413 [PMID: 27038995 DOI: 10.1016/j.ejso.2016.02.257]
33 **Gronchi A**, Fiore M, Miselli F, Lagonigro MS, Coco P, Messina A, Pilotti S, Casali PG. Surgery of residual disease following molecular-targeted therapy with imatinib mesylate in advanced/metastatic GIST. *Ann Surg* 2007; **245**: 341-346 [PMID: 17435538 DOI: 10.1097/01.sla.0000242710.36384.1b]
34 **de Jong MC**, Tsai S, Cameron JL, Wolfgang CL, Hirose K, van Vledder MG, Eckhauser F, Herman JM, Edil BH, Choti MA, Schulick RD, Pawlik TM. Safety and efficacy of curative intent surgery for peri-ampullary liver metastasis. *J Surg Oncol* 2010; **102**: 256-263 [PMID: 20740584 DOI: 10.1002/jso.21610]
35 **Ichida H**, Imamura H, Yoshimoto J, Sugo H, Kajiyama Y, Tsurumaru M, Suzuki K, Ishizaki Y, Kawasaki S. Pattern of postoperative recurrence and hepatic and/or pulmonary resection for liver and/or lung metastases from esophageal carcinoma. *World J Surg* 2013; **37**: 398-407 [PMID: 23142988 DOI: 10.1007/s00268-012-1830-7]
36 **Pocard M**, Pouillart P, Asselain B, Salmon R. Hepatic resection in metastatic breast cancer: results and prognostic factors. *Eur J Surg Oncol* 2000; **26**: 155-159 [PMID: 10744935 DOI: 10.1053/ejso.1999.0761]
37 **Elias D**, Maisonnette F, Druet-Cabanac M, Ouellet JF, Guinebretiere JM, Spielmann M, Delaloge S. An attempt to clarify indications for hepatectomy for liver metastases from breast cancer. *Am J Surg* 2003; **185**: 158-164 [PMID: 12559448 DOI: 10.1016/S0002-9610(02)01204-7]
38 **Adam R**, Aloia T, Krissat J, Bralet MP, Paule B, Giacchetti S, Delvart V, Azoulay D, Bismuth H, Castaing D. Is liver resection justified for patients with hepatic metastases from breast cancer? *Ann Surg* 2006; **244**: 897-907; discussion 907-908 [PMID: 17122615 DOI: 10.1097/01.sla.0000246847.02058.1b]
39 **Hoffmann K**, Franz C, Hinz U, Schirmacher P, Herfarth C, Eichbaum M, Büchler MW, Schemmer P. Liver resection for multimodal treatment of breast cancer metastases: identification of prognostic factors. *Ann Surg Oncol* 2010; **17**: 1546-1554 [PMID: 20143267 DOI: 10.1245/s10434-010-0931-5]
40 **Abbott DE**, Brouquet A, Mittendorf EA, Andreou A, Meric-Bernstam F, Valero V, Green MC, Kuerer HM, Curley SA, Abdalla EK, Hunt KK, Vauthey JN. Resection of liver metastases from breast cancer: estrogen receptor status and response to chemotherapy before metastasectomy define outcome. *Surgery* 2012; **151**: 710-716 [PMID: 22285778 DOI: 10.1016/j.surg.2011.12.017]
41 **Mariani P**, Servois V, De Rycke Y, Bennett SP, Feron JG, Almubarak MM, Reyal F, Baranger B, Pierga JY, Salmon RJ. Liver metastases from breast cancer: Surgical resection or not? A case-matched control study in highly selected patients. *Eur J Surg Oncol* 2013; **39**: 1377-1383 [PMID: 24126165 DOI: 10.1016/j.ejso.2013.09.021]
42 **Sadot E**, Lee SY, Sofocleous CT, Solomon SB, Gönen M, Peter Kingham T, Allen PJ, DeMatteo RP, Jarnagin WR, Hudis CA, D' Angelica MI. Hepatic Resection or Ablation for Isolated Breast Cancer Liver Metastasis: A Case-control Study With Comparison to Medically Treated Patients. *Ann Surg* 2016; **264**: 147-154 [PMID: 26445472 DOI: 10.1097/SLA.0000000000001371]
43 **Neuman HB**, Morrogh M, Gonen M, Van Zee KJ, Morrow M, King TA. Stage IV breast cancer in the era of targeted therapy: does surgery of the primary tumor matter? *Cancer* 2010; **116**: 1226-1233 [PMID: 20101736 DOI: 10.1002/cncr.24873]
44 **Pawlik TM**, Zorzi D, Abdalla EK, Clary BM, Gershenwald JE, Ross MI, Aloia TA, Curley SA, Camacho LH, Capussotti L, Elias D, Vauthey JN. Hepatic resection for metastatic melanoma: distinct patterns of recurrence and prognosis for ocular versus cutaneous disease. *Ann Surg Oncol* 2006; **13**: 712-720 [PMID: 16538410 DOI: 10.1245/ASO.2006.01.016]
45 **Mariani P**, Piperno-Neumann S, Servois V, Berry MG, Dorval T, Plancher C, Couturier J, Levy-Gabriel C, Lumbroso-Le Rouic L, Desjardins L, Salmon RJ. Surgical management of liver metastases from uveal melanoma: 16 years' experience at the Institut Curie. *Eur J Surg Oncol* 2009; **35**: 1192-1197 [PMID: 19329272 DOI: 10.1016/j.ejso.2009.02.016]
46 **Mariani P**, Almubarak MM, Kollen M, Wagner M, Plancher C, Audollent R, Piperno-Neumann S, Cassoux N, Servois V. Radiofrequency ablation and surgical resection of liver metastases from uveal melanoma. *Eur J Surg Oncol* 2016; **42**: 706-712 [PMID: 26968227 DOI: 10.1016/j.ejso.2016.02.019]
47 **Agarwala SS**, Eggermont AM, O'Day S, Zager JS. Metastatic melanoma to the liver: a contemporary and comprehensive review of surgical, systemic, and regional therapeutic options. *Cancer* 2014; **120**: 781-789 [PMID: 24301420 DOI: 10.1002/cncr.28480]
48 **Lang H**, Nussbaum KT, Kaudel P, Frühauf N, Flemming P, Raab R. Hepatic metastases from leiomyosarcoma: A single-center experience with 34 liver resections during a 15-year period. *Ann Surg* 2000; **231**: 500-505 [PMID: 10749609 DOI: 10.1097/00000658-200004000-00007]
49 **Pawlik TM**, Vauthey JN, Abdalla EK, Pollock RE, Ellis LM, Curley SA. Results of a single-center experience with resection and ablation for sarcoma metastatic to the liver. *Arch Surg* 2006; **141**: 537-543; discussion 543-544 [PMID: 16785353 DOI: 10.1001/archsurg.141.6.537]
50 **Marudanayagam R**, Sandhu B, Perera MT, Bramhall SR, Mayer D, Buckels JA, Mirza DF. Liver resection for metastatic soft tissue sarcoma: an analysis of prognostic factors. *Eur J Surg Oncol* 2011; **37**: 87-92 [PMID: 21163386 DOI: 10.1016/j.ejso.2010.11.006]
51 **Zhang F**, Wang J. Clinical Features of Surgical Resection for Liver Metastasis from Extremity Soft Tissue Sarcoma. *Hepatogastroenterology* 2015; **62**: 677-682 [PMID: 26897953]
52 **Thelen A**, Jonas S, Benckert C, Lopez-Hänninen E, Rudolph B, Neumann U, Neuhaus P. Liver resection for metastases from renal cell carcinoma. *World J Surg* 2007; **31**: 802-807 [PMID: 17354021 DOI: 10.1007/s00268-007-0685-9]
53 **Staehler MD**, Kruse J, Haseke N, Stadler T, Roosen A, Karl A, Stief CG, Jauch KW, Bruns CJ. Liver resection for metastatic disease prolongs survival in renal cell carcinoma: 12-year results from a retrospective comparative analysis. *World J Urol* 2010; **28**: 543-547 [PMID: 20440505 DOI: 10.1007/s00345-010-0560-4]
54 **Ruys AT**, Tanis PJ, Nagtegaal ID, van Duijvendijk P, Verhoef C, Porte RJ, van Gulik TM. Surgical treatment of renal cell cancer

liver metastases: a population-based study. *Ann Surg Oncol* 2011; **18**: 1932-1938 [PMID: 21347794 DOI: 10.1245/s10434-010-1526-x]
55 **Hatzaras I**, Gleisner AL, Pulitano C, Sandroussi C, Hirose K, Hyder O, Wolfgang CL, Aldrighetti L, Crawford M, Choti MA, Pawlik TM. A multi-institution analysis of outcomes of liver-directed surgery for metastatic renal cell cancer. *HPB* (Oxford) 2012; **14**: 532-538 [PMID: 22762401 DOI: 10.1111/j.1477-2574.2012.00495.x]
56 **Kamel SI**, de Jong MC, Schulick RD, Diaz-Montes TP, Wolfgang CL, Hirose K, Edil BH, Choti MA, Anders RA, Pawlik TM. The role of liver-directed surgery in patients with hepatic metastasis from a gynecologic primary carcinoma. *World J Surg* 2011; **35**: 1345-1354 [PMID: 21452068 DOI: 10.1007/s00268-011-1074-y]
57 **Merideth MA**, Cliby WA, Keeney GL, Lesnick TG, Nagorney DM, Podratz KC. Hepatic resection for metachronous metastases from ovarian carcinoma. *Gynecol Oncol* 2003; **89**: 16-21 [PMID: 12694649 DOI: 10.1016/S0090-8258(03)00004-0]
58 **Lim MC**, Kang S, Lee KS, Han SS, Park SJ, Seo SS, Park SY. The clinical significance of hepatic parenchymal metastasis in patients with primary epithelial ovarian cancer. *Gynecol Oncol* 2009; **112**: 28-34 [PMID: 19010521 DOI: 10.1016/j.ygyno.2008.09.046]
59 **Neumann UP**, Fotopoulou C, Schmeding M, Thelen A, Papanikolaou G, Braicu EI, Neuhaus P, Sehouli J. Clinical outcome of patients with advanced ovarian cancer after resection of liver metastases. *Anticancer Res* 2012; **32**: 4517-4521 [PMID: 23060580]
60 **Niu GC**, Shen CM, Cui W, Li Q. Hepatic Resection is Safe for Metachronous Hepatic Metastases from Ovarian Cancer. *Cancer Biol Med* 2012; **9**: 182-187 [PMID: 23691476 DOI: 10.7497/j.issn.2095-3941.2012.03.005]
61 **Kolev V**, Pereira EB, Schwartz M, Sarpel U, Roayaie S, Labow D, Momeni M, Chuang L, Dottino P, Rahaman J, Zakashansky K. The role of liver resection at the time of secondary cytoreduction in patients with recurrent ovarian cancer. *Int J Gynecol Cancer* 2014; **24**: 70-74 [PMID: 24356412 DOI: 10.1097/IGC.0000000000000026]
62 **Bacalbasa N**, Dima S, Brasoveanu V, David L, Balescu I, Purnichescu-Purtan R, Popescu I. Liver resection for ovarian cancer liver metastases as part of cytoreductive surgery is safe and may bring survival benefit. *World J Surg Oncol* 2015; **13**: 235 [PMID: 26243426 DOI: 10.1186/s12957-015-0652-0]
63 **Hahn TL**, Jacobson L, Einhorn LH, Foster R, Goulet RJ. Hepatic resection of metastatic testicular carcinoma: a further update. *Ann Surg Oncol* 1999; **6**: 640-644 [PMID: 10560848 DOI: 10.1007/s10434-999-0640-0]

P- Reviewer: Arigami T, Kamiyama T, Wang GY **S- Editor**: Qiu S **L- Editor**: A **E- Editor**: Li D

World Journal of Hepatology

Submit a Manuscript: http://www.wjgnet.com/esps/

World J Hepatol 2017 February 18; 9(5): 252-262

DOI: 10.4254/wjh.v9.i5.252

ISSN 1948-5182 (online)

ORIGINAL ARTICLE

Retrospective Study

Efficacy and safety of telaprevir- and simeprevir-based triple therapies for older patients with chronic hepatitis C

Satoshi Yamagiwa, Toru Ishikawa, Nobuo Waguri, Soichi Sugitani, Hiroto Wakabayashi, Shogo Ohkoshi, Takashi Tsukishiro, Toru Takahashi, Toshiaki Watanabe, Shuji Terai

Satoshi Yamagiwa, Shuji Terai, Division of Gastroenterology and Hepatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata 951-8510, Japan

Toru Ishikawa, Department of Gastroenterology and Hepatology, Saiseikai Niigata Daini Hospital, Niigata 950-1104, Japan

Nobuo Waguri, Department of Gastroenterology and Hepatology, Niigata City General Hospital, Niigata 950-1197, Japan

Soichi Sugitani, Department of Gastroenterology and Hepatology, Tachikawa General Hospital, Nagaoka 940-8621, Japan

Hiroto Wakabayashi, Department of Gastroenterology and Hepatology, Takeda General Hospital, Aizuwakamatsu 965-8585, Japan

Shogo Ohkoshi, Department of Internal Medicine, Nippon Dental University Medical Hospital, Niigata 951-8580, Japan

Takashi Tsukishiro, Department of Internal Medicine, Itoigawa General Hospital, Itoigawa 941-8502, Japan

Toru Takahashi, Department of Internal Medicine, Uonuma Hospital, Ojiya 947-0028, Japan

Toshiaki Watanabe, Watanabe Clinic, Sanjyo 955-0845, Japan

Author contributions: Yamagiwa S, Ishikawa T, Waguri N and Terai S contributed to study conception and design; Yamagiwa S, Sugitani S, Wakabayashi H, Ohkoshi S, Tsukishiro T, Takahashi T and Watanabe T contributed to data acquisition, data analysis and interpretation; Yamagiwa S and Terai S contributed to drafting the article; all authors contributed to making critical revisions related to important intellectual content of the manuscript; all authors contributed to final approval of the version of the article to be published.

Supported by Grants-in-Aid for Scientific Research (C) (to Yamagiwa S) from Japan Society for the Promotion of Science (JSPS), No. 15K08991.

Institutional review board statement: The study was reviewed and approved by Niigata University Medical and Dental Hospital Institutional Review Board.

Informed consent statement: Written informed consent under institutional review board-approved protocols (approval no. 1474) at Niigata University Medical and Dental Hospital was appropriately obtained from all the individuals enrolled in the study.

Conflict-of-interest statement: We have no financial relationships to disclose.

Data sharing statement: No additional data are available.

Manuscript source: Unsolicited manuscript

Correspondence to: Satoshi Yamagiwa, MD, PhD, Associate Professor, Division of Gastroenterology and Hepatology, Niigata University Graduate School of Medical and Dental Sciences, 1-757 Asahimachi-dori, Chuo-ku, Niigata 951-8510, Japan. syamagi@med.niigata-u.ac.jp
Telephone: +81-25-2272207
Fax: +81-25-2270776

Received: August 22, 2016
Peer-review started: August 24, 2016
First decision: September 27, 2016
Revised: December 29, 2016
Accepted: January 11, 2017
Article in press: January 14, 2017
Published online: February 18, 2017

Abstract

AIM

To evaluate and compare the efficacy and safety of telaprevir (TVR)-and simeprevir (SMV)-based triple therapies in elderly patients, specifically patients aged 66 years or older.

METHODS

The present study enrolled 112 and 76 Japanese patients with chronic hepatitis C virus genotype 1b infection who were treated with a 12-wk TVR-based or SMV-based triple therapy, respectively, followed by a dual therapy that included pegylated interferon α and ribavirin (RBV) for 12 wk. The patients were categorized into two groups according to age as follows: A younger group of patients aged ≤ 65 years old and an older group of patients aged > 65 years old. Among the patients treated with TVR-based triple therapy, 34 patients were included in the older group. The median ages were 56 years (range: 28-65 years) in the younger group and 69 years (range: 66-81 years) in the older group. Among the patients treated with SMV-based triple therapy, 39 patients were included in the older group. The median ages were 59 years (range: 36-65 years) in the younger group and 71 years (range: 66-86 years) in the older group. The clinical, biochemical and virological data were analyzed before and during treatment.

RESULTS

Among the patients treated with the TVR-based triple therapy, no significant difference in the sustained virological response (SVR) was found between the younger (80.8%) and older (88.2%) groups. The SVR rates for patients with the interleukin 28B (IL28B) (rs8099917) TG/GG-genotypes (73.9% and 60.0% in the younger and older groups, respectively) were significantly lower than for patients with the IL28B TT-genotype (86.3% and 92.9%, respectively). The cumulative exposure to RBV for the entire 24-wk treatment period (as a percentage of the target dose) was significantly higher in the younger group than in the older group (91.7% *vs* 66.7%, respectively, $P < 0.01$), but the cumulative exposure to TVR was not significantly different between the younger and older groups (91.6% *vs* 81.9%, respectively). A multivariate analysis identified the TT-genotype of IL28B (OR = 8.160; 95%CI: 1.593-41.804, $P = 0.012$) and the adherence of RBV (> 60%) (OR = 11.052; 95%CI: 1.160-105.273, $P = 0.037$) as independent factors associated with the SVR. Adverse events resulted in discontinuation of the treatment in 11.3% and 14.7% of the younger and older groups, respectively. Among the patients treated with the SMV-based triple therapy, no significant difference in the SVR rare was found between the younger (81.1%) and older (82.1%) groups. The SVR rates for patients with the IL28B TG/GG-genotypes (77.8% and 64.7% in the younger and older groups, respectively) were significantly lower than for patients with the IL28B TT-genotype (88.2% and 100%, respectively). A multivariate analysis identified the TT-genotype of IL28B as an independent factor associated with the SVR (OR = 9.677; 95%CI: 1.114-84.087, $P = 0.040$). Adverse events resulted in discontinuation of the treatment in 7.0% and 14.3% of patients in the younger and older groups, respectively.

CONCLUSION

Both TVR- and SMV-based triple therapies can be successfully used to treat patients aged 66 years or older with genotype 1b chronic hepatitis C. Genotyping of the IL28B indicates a potential to achieve SVR in these difficult-to-treat elderly patients.

Key words: Telaprevir; Aged patients; Hepatitis C virus genotype 1b; Interleukin 28B; Simeprevir

Core tip: We evaluated the efficacy and safety of telaprevir (TVR)-and simeprevir (SMV)-based triple therapies for elderly patients with chronic hepatitis C, especially patients aged 66 years or older, in a real-world clinical setting. In both the TVR and SMV groups, no significant differences in the SVR and adverse events resulting in treatment discontinuation were found between the younger (aged ≤ 65) and older (aged > 65) patients. Both the TVR- and SMV-based triple therapies can be successfully used to treat patients aged 66 years or older with chronic hepatitis C virus genotype 1b infection. Genotyping of the interleukin-28B indicates a potential to achieve SVR in these difficult-to-treat elderly patients.

Yamagiwa S, Ishikawa T, Waguri N, Sugitani S, Wakabayashi H, Ohkoshi S, Tsukishiro T, Takahashi T, Watanabe T, Terai S. Efficacy and safety of telaprevir- and simeprevir-based triple therapies for older patients with chronic hepatitis C. *World J Hepatol* 2017; 9(5): 252-262 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i5/252.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i5.252

INTRODUCTION

Chronic hepatitis C virus (HCV) infections affect approximately 130-170 million people worldwide and are associated with an increased risk of developing liver cirrhosis and hepatocellular carcinoma (HCC)[1,2]. In Japan, an estimated 1.5-2 million people are infected with HCV[3]. Most of infected patients in Japan are infected with genotype 1 HCV and are older than the infected patients in Europe and the United States[4]. Although older patients with chronic HCV infection have a higher risk of developing HCC than younger patients even at the same liver fibrosis stage[5], older patients have been reported to show poor virological responses to antiviral treatments, especially postmenopausal women[6-8]. Because older patients often have reduced cardiovascular, pulmonary, and renal function and a decreased blood count, they are usually more susceptible to the toxic effects of antiviral treatments, which may lead to a higher rate and severity of adverse events and a poor adherence to the treatment[4]. Therefore, an evaluation of the safety and efficacy of antiviral treatments, especially in elderly patients with chronic HCV infections, is still necessary.

Before the introduction of direct-acting antiviral agents (DAA), pegylated interferon (PegIFN) α and ribavirin (RBV) were the standard of care for HCV genotype 1 infections. However, with the approval of telaprevir (TVR) that is an HCV non-structural (NS) 3/4A protease inhibitor, the optimum treatment regimen for chronic HCV genotype 1 infections was changed to a triple therapy with a protease inhibitor plus PegIFN α and RBV for 24 wk[9]. The TVR-based triple therapy has achieved an improved sustained virological response (SVR) rate compared to PegIFN monotherapy or PegIFNα plus RBV dual therapy[10,11]. However, the TVR-based triple therapy is associated with an increased rate and severity of adverse events, including pruritus, skin rash, anemia, and anorectal diseases, as well as increased rates of treatment discontinuation compared to patients receiving PegIFNα plus RBV dual therapy[10,11]. Because of the increased risk and severity of adverse events associated with the TVR-based triple therapy, it is difficult to use this therapy in older patients, and, therefore, reports describing the safety and efficacy of TVR-based triple therapy in elderly patients are limited[4].

Simeprevir (SMV) is a second-generation oral HCV NS3/4A protease inhibitor with antiviral activity against HCV genotype 1, 2, 4, 5 and 6 infections[12]. The QUEST 1 and QUEST 2 phase 3 clinical trials demonstrated the SVR rates of 80% and 81%, respectively, in patients treated with SMV-based triple therapy combined with PegIFNα and RBV[13]. In Japan, 4 phase 3 clinical trials (CONCERTO) were conducted, and the SVR rates were 88.6% and 91.7% for treatment-naïve patients; 35.8%, 50.9% and 38.5% for non-responders; and 89.8% and 96.6% for patients that relapsed[14-16]. Although the SMV-based triple therapy shows a favorable efficacy without inducing severe dermatologic and hematologic toxicities, the safety and efficacy of the SMV-based triple therapy for elderly patients has not yet been fully evaluated. Therefore, in the present study, we aimed to assess the efficacy and safety of TVR- and SMV-based triple therapies in elderly patients, specifically patients aged 66 years or older, in a real-world clinical setting.

MATERIALS AND METHODS

Patients

This prospective and multicenter study enrolled 112 and 76 HCV genotype 1b Japanese patients who received 12 wk of TVR-based and SMV-based triple therapies, respectively, followed by a dual therapy that included PegIFNα and RBV for 12 wk. Nine hospitals in Niigata, Japan, including Niigata University Hospital, participated in this study. The patients were categorized into two groups according to age as follows: A younger group of patients aged ≤ 65 years old and an older group of patients aged > 65 years old. Among the patients treated with the TVR-based triple therapy, 34 patients were included in the older group. The median ages were 56 years (range: 28-65 years) in the younger group and 69 years (range: 66-81 years) in the older group. Among the patients treated with the SMV-based triple therapy, the older group consists of 39 patients. The median ages were 59 years (range: 36-65 years) in the younger group and 71 years (range: 66-86 years) in the older group. Liver biopsy samples were obtained from 34 (30.6%) and 42 patients (55.2%) in the TVR and SMV groups, respectively. For each sample, the fibrosis stage (F0-4) and activity grade (A0-3) were evaluated according to the Metavir score[17].

According to responses to prior treatments, relapse was defied as undetectable HCV during and at the end of treatment with positive HCV RNA detecting later on. Non-responder was defined as detectable HCV RNA for more than 24 wk. Patients with decompensated liver cirrhosis, hepatocellular carcinoma, co-infection with hepatitis B virus or human immunodeficiency virus, autoimmune hepatitis, primary biliary cirrhosis, hemochromatosis, or Wilson's disease were excluded. Patients with uncontrollable diabetes mellitus, chronic renal failure, depression, and those with a history of alcohol abuse, were also excluded. Information regarding patient profiles was shown in Tables 1 and 2.

Study design

All patients received a 12-wk triple therapy that included either TVR [1500 or 2250 mg/d; the initial dose of TVR was determined by each attending physician based on each patient's baseline characteristics such as bodyweight (BW)] (the dose of TVR was also reduced by each attending physician based on each patient's adverse events such as anemia, malaise, and anorexia) (Telavic; Mitsubishi Tanabe Pharma, Osaka, Japan) or SMV (100 mg/d) (Sovriad; Janssen Pharmaceutical K.K., Tokyo, Japan) combined with PegIFNα2a (180 μg/wk) (Pegasys; Chugai Pharmaceutical Co., Ltd., Tokyo, Japan) or PegIFNα2b (1.5 μg/BW kg per week) (Peg-Intron; MSD, Tokyo, Japan) and RBV (600-1000 mg/d according to BW as follows: < 60 kg: 600 mg/d; 60-80 kg: 800 mg/d; > 80 kg: 1000 mg/d; if the patient's hemoglobin was < 13 g/dL at the start of therapy, RBV was reduced by 200 mg) (Rebetol; MSD or Copegus; Chugai Pharmaceutical Co., Ltd.), followed by dual therapy of PegIFNα2a or PegIFNα2b with RBV for 12 wk.

This study was conducted in accordance with the Declaration of Helsinki. The study was reviewed and approved by the Niigata University Medical and Dental Hospital Institutional Review Board. Written informed consent was appropriately obtained from all of the individuals who enrolled in the study according to the institutional review board's approved protocols (approval No. 1474) at the Niigata University Medical and Dental Hospital.

Table 1 Patient characteristics by age (telaprevir)

Factors (median, range)	Patients aged < 66	Patients aged ⩾ 66	*P* value
n	78	34	
Gender, *n* (male/female)	41/37	20/14	0.68
Age (yr)	56 (28-65)	69 (66-81)	< 0.001
Body weight (kg)	61.1 (35.0-97.4)	57.8 (41.0-74.8)	0.105
Body mass index (kg/m^2)	22.7 (15.8-32.2)	22.9 (17.9-28.9)	0.892
Baseline HCV-RNA (log IU/mL)	6.7 (3.9-7.7)	6.7 (3.1-7.8)	0.766
White blood cell (/mm^3)	5000 (1900-8720)	4500 (2700-7700)	0.245
Hemoglobin (g/dL)	14.0 (9.1-18.6)	13.5 (9.5-16.3)	0.121
Platelets (× 10^4/mm^3)	15.8 (6.5-28.7)	13.4 (8.3-29.0)	0.068
Albumin (mg/dL)	4.1 (2.7-5.9)	3.9 (2.4-4.4)	0.007
AST (IU/L)	40 (17-249)	45 (20-163)	0.909
ALT (IU/L)	48 (15-278)	38 (15-189)	0.486
γ-GTP (IU/L)	39 (11-717)	25 (11-144)	0.034
Serum creatinine (mg/dL)	0.7 (0.4-1.2)	0.8 (0.4-1.0)	0.036
Estimated GFR (mL/min)	79.0 (44.0-134.0)	71.5 (39.0-101.9)	0.006
Prior treatment response, *n* (naïve/relapse/non-responder)	45/26/7	15/15/4	0.403
Liver histology (F0-2/3-4/ND)	21/6/51	4/3/27	0.348
IL28B SNP (rs8099917), *n* (TT/non-TT/ND)	51/22/5	28/5/1	0.235
HCV ISDR, *n* (0/1-3 /4-/NT)	32/26/6/14	15/10/2/7	0.955
HCV Core 70, *n* (Wild/Mutant/ND)	46/18/14	18/10/6	0.751
HCV Core 91, *n* (Wild/Mutant/ND)	42/22/14	19/9/6	1
Serum CXCL10 (pg/mL)	510 (95-1794)	543 (118-1218)	0.445

GFR: Glomerular filtration rate; IL28B SNP: Interleukin-28B single nucleotide polymorphism; ND: Not determined; ISDR: Interferon sensitivity-determining region; HCV Core 70 or 91: At position 70 or 91 of the HCV core protein; CXCL10: Chemokine (C-X-C motif) ligand 10; HCV: Hepatitis C virus; AST: Aspartate transaminase; ALT: Alanine aminotransferase; γ-GTP: γ-glutamyl-transpeptidase.

Table 2 Patient characteristics by age (simeprevir)

Factors (median, range)	Patients aged < 66	Patients aged ⩾ 66	*P* value
n	37	39	-
Gender, *n* (%) (male/female)	19/18 (48.6)	14/25 (64.1)	0.123
Age (yr)	59 (36-65)	71 (66-86)	< 0.001
Body weight (kg)	62.0 (39.8-94.0)	56.0 (37.5-76.6)	0.011
Body mass index (kg/m^2)	22.8 (17.2-30.3)	22.7 (17.8-32.1)	0.287
Baseline HCV-RNA (log IU/mL)	6.7 (5.4-7.8)	6.6 (4.7-7.6)	0.631
White blood cells (/mm^3)	4620 (2600-7800)	4300 (2400-8100)	0.010
Hemoglobin (g/dL)	13.8 (11.0-16.7)	13.1 (9.8-16.8)	< 0.001
Platelets (× 10^4/mm^3)	16.4 (8.7-28.8)	16.3 (7.3-31.7)	0.291
Albumin (mg/dL)	4.2 (2.8-4.8)	4.0 (3.1-4.6)	0.002
AST (IU/L)	45 (21-159)	34 (19-128)	0.056
ALT (IU/L)	42 (16-316)	29 (12-112)	0.006
γ-GTP (IU/L)	29 (13-260)	27 (9-171)	0.388
Serum creatinine (mg/dL)	0.70 (0.44-1.01)	0.70 (0.42-1.36)	0.689
Estimated GFR (mL/min)	78.7 (50.0-112.6)	77.4 (41.3-109.0)	0.221
Prior treatment response, *n* (naïve/relapse/non-responder)	20/10/7	13/16/10	0.197
Liver histology (F0-2/3-4/ND)	12/6/19	19/5/15	0.483
IL28B SNP (rs8099917), *n* (TT/non-TT/ND)	17/19/1	18/17/4	1
HCV ISDR, *n* (0/1-3/4-/ND)	9/13/5/10	11/12/2/14	0.044
HCV Core 70, *n* (Wild/Mutant/ND)	17/13/7	15/8/16	1
HCV Core 91, *n* (Wild/Mutant/ND)	18/12/7	18/5/16	0.385

GFR: Glomerular filtration rate; IL28B SNP: Interleukin-28B single nucleotide polymorphism; ND: Not determined; ISDR: Interferon sensitivity-determining region; HCV core 70 or 91: At position 70 or 91 of the HCV core protein; HCV: Hepatitis C virus; AST: Aspartate transaminase; ALT: Alanine aminotransferase; γ-GTP: γ-glutamyl-transpeptidase.

Laboratory and safety assessments

Laboratory and safety assessments were performed at initiation of treatment; at treatment weeks 2, 4, 8, 12, 16, 20 and 24; at the end of treatment; and at 12 and 24 wk after the end of treatment. Data on adverse events were collected, and physical examinations were performed at each visit, if clinically indicated.

Detection of HCV markers

The detection of HCV viremia was performed using a real-time polymerase chain reaction assay (COBAS TaqMan HCV test, Roche Diagnostic, Tokyo, Japan) with

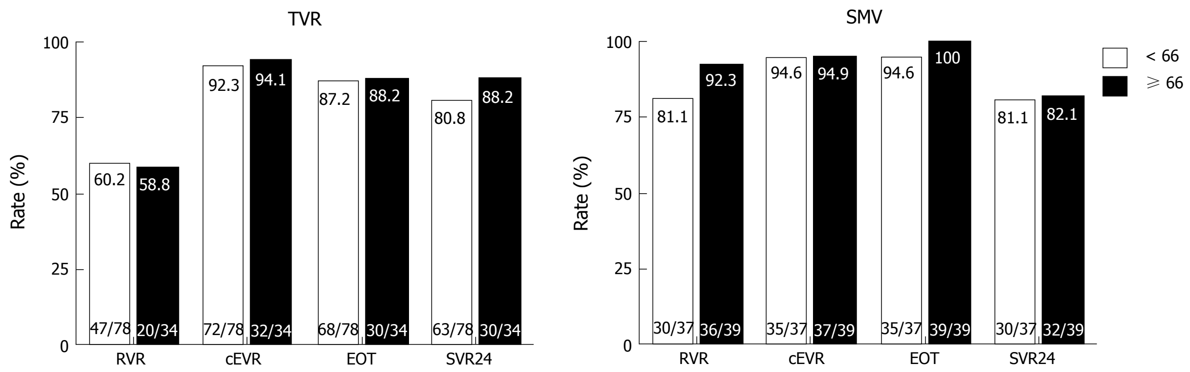

Figure 1 Rates of virological responses to telaprevir and simeprevir by age. Percentages indicate the proportion of patients with undetectable serum hepatitis C virus (HCV) RNA levels. Patient numbers are shown in parenthesis. TVR: Telaprevir; SMV: Simeprevir; RVR: Rapid virological response; cEVR: Complete early virological response; EOT: End of treatment response; SVR24: Sustained virological response defined as undetectable serum HCV RNA at 24 wk after the end of treatment.

a lower limit of quantitation of 15 IU/mL and a linear dynamic range of 1.2-7.8 log IU/mL. The number of amino acid substitutions in the interferon sensitivity-determining region (in the range of 2209-2248 in the HCV NS5A) was determined using a direct sequencing method as reported previously[18]. The core amino acid substitutions at positions 70 and 91 of the HCV genome were determined by direct sequencing as reported previously[19].

Treatment efficacy

SVR that is defined as undetectable serum HCV RNA at 24 wk after the end of treatment was successful treatment. Early virological responses during the first 12 wk of treatment were defined as rapid virological response (RVR), which was undetectable HCV RNA at week 4, and complete early virological response (cEVR), which was undetectable at week 12. End of treatment response (ETR) was defined as undetectable HCV RNA at the end of treatment. Relapse was defined as an ETR response but non-SVR.

Interleukin 28B single-nucleotide polymorphism

Human genomic DNA was extracted from the peripheral blood. Single-nucleotide polymorphism (SNP) genotyping of the interleukin 28B (IL28B) (rs8099917) gene was performed using the TaqMan allelic discrimination demonstration kit (Applied Biosystems, Foster City, CA). The rs8099917 genotype was classified into the following 2 categories: TT (major genotype) and non-TT (minor genotype, TG or GG).

Statistical analysis

Continuous data from patients are expressed as the median with the interquartile range. The significance of the differences was analyzed statistically by the χ^2, Fisher's exact test, or Mann-Whitney *U* test, as appropriate, using SPSS software (Ver.18, SPSS Inc., Chicago, IL). To evaluate independent factors for predicting an SVR, variables that reached the $P < 0.1$ level in the univariate tests were used as candidate factors in a multivariate logistic regression analysis. In all of the cases, the level of significance was set as P value < 0.05.

RESULTS

Patient characteristics

The patient characteristics in the TVR group (n = 112) and SMV group (n = 76) are summarized by age in Tables 1 and 2. The analysis of the pretreatment factors revealed that serum albumin, γ-glutamyl-transpeptidase, and the estimated glomerular filtration rate in the older patients were significantly lower than those of the younger patients in the TVR group (Table 1). Pretreatment serum chemokine C-X-C motif ligand 10 (CXCL10) levels were not significantly different between the younger (543 pg/mL, range: 118-1218 pg/mL) and older (510 pg/mL, range: 95-1794 pg/mL) groups. In the SMV group, BW, white blood cell count, hemoglobin, serum albumin, and serum alanine aminotransferase (ALT) in the older patients were significantly lower than those of the younger patients (Table 2). No significant differences in the prior treatment response, HCV core 70/91 mutations, or IL28B SNPs were found between the younger and older group in both TVR and SMV groups.

Virological response and outcome

Figure 1 shows the virological responses by age. RVR, cEVR, ETR and SVR did not significantly differ between the younger and older patients in the TVR group (60.2% *vs* 58.8%, 92.3% *vs* 94.1%, 87.2% *vs* 88.2%, and 80.8% *vs* 88.2%, respectively). Similar to the TVR group, RVR, cEVR, ETR and SVR did not significantly differ between the younger and older patients in the SMV group (81.1% *vs* 92.3%, 94.6% *vs* 94.9%, 94.6% *vs* 100% and 81.1% *vs* 82.1%, respectively). In the older patients, SVR did not significantly differ between the TVR and SMV groups, although RVR was significantly higher in the SMV group than in the TVR group (92.3% *vs* 58.5%, $P < 0.01$).

Figure 2 shows the virological responses according to prior treatment responses. In both the TVR and SMV groups, SVR did not significantly differ between the younger and older patients with the same treatment responses. In the older patients in the SMV group, SVR

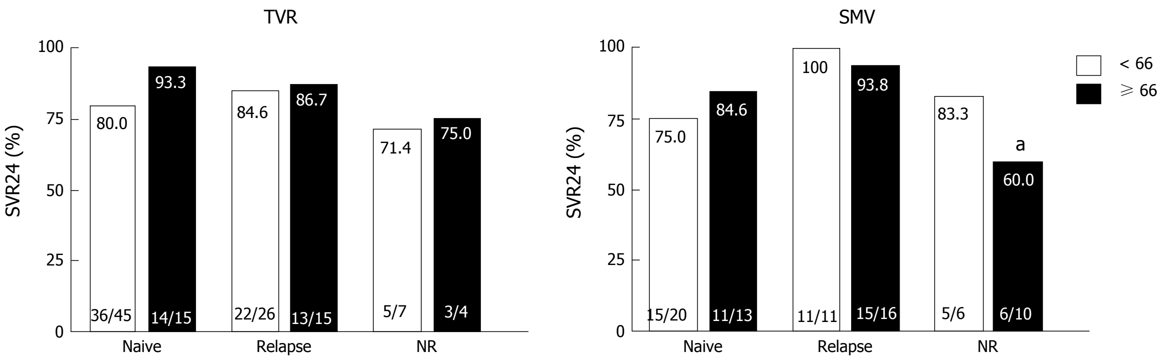

Figure 2 Rates of sustained virological response to telaprevir and simeprevir by prior treatment responses. Percentages indicate the proportion of patients with undetectable serum hepatitis C virus (HCV) RNA levels at 24 wk after the end of treatment. Patient numbers are shown in parenthesis. [a]P = 0.033 (compared to relapsers in the older patients). NR: Non-responders; TVR: Telaprevir; SMV: Simeprevir; SVR24: Sustained virological response defined as undetectable serum HCV RNA at 24 wk after the end of treatment.

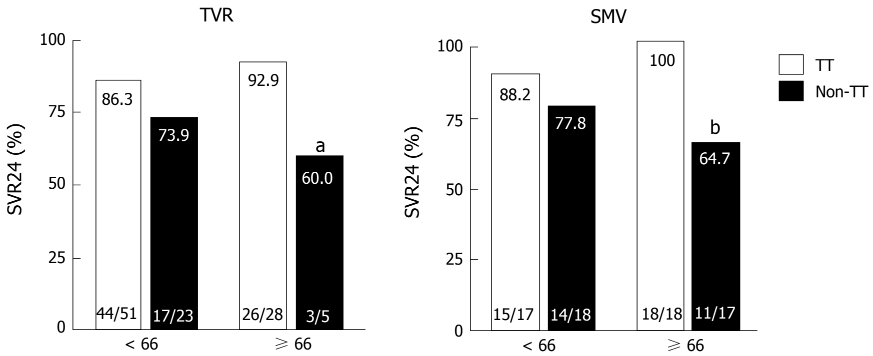

Figure 3 Rates of sustained virological response to telaprevir and simeprevir by interleukin 28B single-nucleotide polymorphism. Percentages indicate the proportion of patients with undetectable serum hepatitis C virus RNA levels at 24 wk after the end of treatment. Patient numbers are shown in parenthesis. TT, interleukin 28B (IL28B) (rs8099917) TT-genotype; non-TT, IL28B TG/GG-genotypes [a]P = 0.038 (compared to older patients with the IL28B TT-genotype). [b]P = 0.005 (compared to older patients with the IL28B TT-genotype). TVR: Telaprevir; SMV: Simeprevir; SVR24: Sustained virological response defined as undetectable serum HCV RNA at 24 wk after the end of treatment.

was significantly lower in the prior non-responders than the prior relapsers (60% *vs* 93.8%, P = 0.033). Figure 3 shows the virological responses according to IL28B (rs8099917) SNP status. In the TVR group, the SVR rate for the older patients with the IL28B TT-genotype was significantly higher than for the older patients with the IL28B TG/GG-genotypes (92.9% and 60%, P = 0.038). In the SMV group, the SVR rate for the older patients with the IL28B TT-genotype was also significantly higher than for the older patients with the IL28B TG/GG-genotypes (100% and 64.7%, P < 0.01).

Safety and tolerability

Treatment tolerability was summarized in Tables 3 and 4. In the TVR group, adverse events resulted in treatment discontinuation in 16.7% (13/78 cases) and 11.8% (4/34 cases) of patients in the younger and older groups, respectively. Although a greater number of older patients in the TVR group was treated with the lower initial dose of TVR (1500 mg/d) than the younger patients (P < 0.01)[20], 9 patients (26.4%) discontinued TVR because of adverse events (four patients experienced skin rush, four patients experienced anemia, and one patient experienced renal dysfunction). However, the rate of discontinuation of TVR did not significantly differ between the younger and older patients (Table 3). The cumulative exposure to RBV for the whole 24-wk treatment period (as a percentage of the target dose) was significantly higher in the younger patients than in the older patients (79.3% ± 26.2% *vs* 62.7% ± 25.3%, P < 0.01), but the cumulative exposure to TVR was not significantly different between the younger and older patients (88.8% ± 22.8% *vs* 83.5% ± 25.5%, P = 0.103). Conversely, SMV was not discontinued in either the younger or older patients, although the rate of discontinuation of RBV was significantly higher in the older patients than the younger patients in the SMV group (58.9% *vs* 29.7%, P = 0.012) because of anemia. Adverse events resulted in treatment discontinuation in 8.1% (3/37 cases) and 7.6% (3/39 cases) of patients in the younger and older groups, respectively.

Predictive factors correlated with SVR24

To identify pretreatment and treatment factors that contribute to SVR, univariate and multivariate analyses were performed in the TVR and SMV groups including the following variables: Gender, age, body mass index, baseline HCV viral load, serum ALT, hemoglobin, platelet

Table 3 Treatment tolerability (telaprevir)

	Patients aged < 66	Patients aged ≥ 66	*P* value
Initial doses (median, range)			
PEG-IFN/BW (μg/kg per week)	1.48 (0.98-2.00)	1.49 (1.15-1.87)	0.859
TVR/BW (mg/kg per day)	33.0 (19.2-64.3)	29.2 (7.5-54.2)	0.044
TVR (2250 mg/1500 mg/others), *n*	55/23/0	11/21/2	< 0.001
RBV/BW (mg/kg per day)	11.4 (6.8-20.0)	11.4 (5.7-28.0)	0.103
Dose reduction, *n* (%)			
PEG-IFN	7 (8.9)	6 (17.6)	0.209
TVR	19 (24.3)	12 (35.3)	0.256
RBV	40 (51.2)	27 (79.4)	0.006
Discontinuation, *n* (%)			
PEG-IFN	13 (16.7)	4 (11.8)	0.580
TVR	12 (15.4)	9 (26.5)	0.192
RBV	12 (15.4)	7 (20.6)	0.585
Adherence, mean ± SD (%)			
PEG-IFN	88.2 ± 25.7	90.1 ± 19.8	0.606
TVR	88.8 ± 22.8	83.5 ± 25.5	0.103
RBV	79.3 ± 26.2	62.7 ± 25.3	< 0.001

PEG-IFN: Pegylated interferon; BW: Bodyweight; TVR: Telaprevir; RBV: Ribavirin.

Table 4 Treatment tolerability (simeprevir)

	Patients aged < 66	Patients aged ≥ 66	*P* value
Initial doses (median, range)			
PEG-IFNα2a (180/90) (μg/wk)	19/0	10/1	0.366
PEG-IFNα2b (120/100/80/others) (μg/wk)	2/16/5/1	0/25/5/1	0.422
SMV/BW (mg/kg per day)	1.6 (1.1-2.5)	1.8 (1.3-2.7)	0.011
RBV/BW (mg/kg per day)	11.6 (6.8-17.1)	12.3 (6.0-20.6)	0.166
Dose reduction, *n* (%)			
PEG-IFN	5 (13.5)	6 (15.3)	1
SMV	0	0	1
RBV	3 (8.1)	6 (15.3)	0.481
Discontinuation, *n* (%)			
PEG-IFN	5 (13.5)	5 (12.8)	1
SMV	2 (5.4)	2 (5.1)	1
RBV	11 (29.7)	23 (58.9)	0.012
Adherence, mean ± SD (%)			
PEG-IFN	93.6 ± 16.8	92.3 ± 19.5	0.592
SMV	98.1 ± 7.2	93.9 ± 18.1	0.079
RBV	91.0 ± 16.1	86.8 ± 20.2	0.126

PEG-IFN: Pegylated interferon; SMV: Simeprevir; BW: Bodyweight; RBV: Ribavirin.

counts, IL28B SNP, initial dose of TVR, TVR/BW (mg/kg per day), SMV/BW (mg/kg per day), dose reduction of treatments, and RVR (Tables 5 and 6). In the TVR group, the IL28B SNP significantly correlated with SVR according to the univariate analysis. A multivariate logistic regression analysis identified the IL28B TT-genotype (OR = 8.160; 95%CI: 1.593-41.804, *P* = 0.012) and the adherence of RBV (> 60%) (OR = 11.052; 95%CI: 1.160-105.273, *P* = 0.037) as independent factors associated with the SVR (Table 5). In the SMV group, the IL28B SNP and the absence of a dose reduction in PegIFN significantly correlated with SVR according to the univariate analysis. In the multivariate logistic regression analysis, the independent factors associated with the SVR were IL28B TT-genotype (OR = 9.677; 95%CI: 1.114-84.087, *P* = 0.040) and the absence of a dose reduction in PegIFN (OR = 6.557; 95%CI: 1.328-32.377, *P* = 0.021) (Table 6).

DISCUSSION

In this study, we evaluated and compared the efficacy and safety of TVR- and SMV-based triple therapies in combination with PegIFN and RBV in elderly Japanese patients with chronic hepatitis C (CHC), specifically patients aged 66 years or older. The rate of SVR did not differ significantly between younger and older patients in either the TVR or the SMV groups. Among the older patients who were more difficult to treat, more patients carrying the IL28B TG/GG genotypes and prior non-responders were enrolled in the SMV group than the TVR group. However, the rate of SVR did not differ significantly between the TVR and SMV group, although the rates of RVR and relapse were significantly higher in

Table 5 Univariate and multivariate analysis of factors contributing to SVR24 (telaprevir)

Factors	Univariate analysis		Multivariate analysis	
	Odds ratio (95%CI)	*P* value	Odds ratio (95%CI)	*P* value
Age	1.012 (0.955-1.072)	0.689		
Gender (female)	0.784 (0.262-2.342)	0.663		
Body mass index (kg/m^2)	1.074 (0.875-1.318)	0.495		
Prior treatment response (non-NR)	3.850 (0.830-17.861)	0.085		
Baseline HCV-RNA (log IU/mL)	1.264 (0.457-3.495)	0.652		
Baseline ALT (IU/mL)	1.008 (0.998-1.017)	0.105		
Baseline platelets (× 10^4/mm^3)	1.017 (0.906-1.142)	0.775		
Baseline hemoglobin (g/dL)	1.038 (0.736-1.464)	0.830		
IL28B SNP (TT)	6.700 (1.826-24.584)	0.004	8.160 (1.593-41.804)	0.012
Initial dose of TVR (2250 mg/d)	2.069 (0.670-6.553)	0.204		
TVR/BW (mg/kg per day)	0.938 (0.870-1.011)	0.093		
RBV/BW (mg/kg per day)	0.811 (0.617-1.066)	0.133		
PEG-IFN dose reduction (none)	2.134 (0.253-17.988)	0.486		
TVR dose reduction (none)	1.020 (0.281-3.703)	0.976		
RBV dose reduction (none)	1.548 (0.433-5.525)	0.501		
Adherence of RBV (> 60%)	6.873 (1.784-26.474)	0.005	11.052 (1.160-105.273)	0.037
RVR (none)	0.88 (0.123-1.216)	0.104		

HCV: Hepatitis C virus; ALT: Alanine aminotransferase; NR: Non-responder; IL28B SNP: Interleukin-28B single nucleotide polymorphism; TVR: Telaprevir; RVR: Rapid virological response; PEG-IFN: Pegylated interferon; BW: Bodyweight; RBV: Ribavirin.

Table 6 Univariate and multivariate analysis of factors contributing to SVR24 (simeprevir)

Factors	Univariate analysis		Multivariate analysis	
	Odds ratio (95%CI)	*P* value	Odds ratio (95%CI)	*P* value
Age	0.998 (0.942-1.058)	0.953		
Gender (female)	0.330 (0.083-1.314)	0.116		
Body mass index (kg/m^2)	1.164 (0.934-1.450)	0.175		
Prior treatment response (non-NR)	2.955 (0.811-10.764)	0.101		
Baseline HCV-RNA (log IU/mL)	0.767 (0.328-1.791)	0.540		
Baseline ALT (IU/mL)	0.998 (0.985-1.012)	0.785		
Baseline platelets (× 10^4/mm^3)	1.082 (0.953-1.228)	0.224		
Baseline hemoglobin (g/dL)	1.257 (0.827-1.910)	0.285		
IL28B SNP (TT)	12.593 (1.516-104.576)	0.019	9.677 (1.114-84.087)	0.040
SMV/BW (mg/kg per day)	0.306 (0.054-1.742)	0.182		
RBV/BW (mg/kg per day)	1.085 (1.138-3.913)	0.501		
PEG-IFN dose reduction (none)	7.250 (1.712-30.700)	0.007	6.557 (1.328-32.377)	0.021
RBV dose reduction (none)	1.556 (0.470-5.160)	0.470		
RVR (none)	0.351 (0.075-1.637)	0.183		

HCV: Hepatitis C virus; ALT: Alanine aminotransferase; NR: Non-responder; IL28B SNP: Interleukin-28B single nucleotide polymorphism; SMV: Simeprevir; BW: Bodyweight; PEG-IFN: Pegylated interferon; RBV: Ribavirin; RVR: Rapid virological response.

the SMV group than the TVR group. When we performed univariate analyses of factors associated with SVR in all the enrolled patients, we did not find any significance in the type of treatment (TVR *vs* SMV) (OR = 1.115, 95%CI: 0.415-3.192, *P* = 0.787). Ogawa *et al*[21] reported that the rates of SVR were similar for patients with HCV genotype 1b who were treated with TVR- and SMV-based triple therapies, although patients treated with TVR-based triple therapy had more frequent severe adverse events than those treated with SMV-based triple therapy. In this study, the rate of adverse events that resulted in treatment discontinuation did not differ between the younger and older patients in either the TVR or the SMV group, although a higher frequency and severity of adverse events have been reported in patients treated with TVR-based triple therapy compared to patients treated with PegIFN and RBV dual therapy[10,11]. We found that both TVR- and SMV-based triple therapy were effective and tolerable among older patients aged 66 years or older.

In Japan, an estimated 1.5-2 million people are infected with HCV, and these patients are older than those infected in Europe and the United States[3,22]. However, previous studies describing the safety and efficacy of TVR- and SMV-based triple therapies, especially in elderly patients with CHC, are limited. One of the reasons may be that the inclusion criteria for clinical trials were usually set to a maximum age of 65 years[11,23]. Furusyo *et al*[4] reported that there were no differences in the efficacy, frequency and severity of adverse events between patients aged > 60 years and those aged ≤ 60 years who were treated with TVR-based triple therapy. Consistent with our study, they reported that a multivariate analysis revealed that the IL28B TT-genotype and the achievement of

RVR were independent factors associated with SVR. Although the decrease in hemoglobin was significantly higher in patients aged > 60 years compared to younger patients aged ≤ 60 years, the rate of adverse events that resulted in treatment discontinuation was similar between the two groups[4]. Abe *et al*[23] also reported that in patients treated with TVR-based triple therapy, the SVR rate in patients aged > 65 years was similar to that of patients aged ≤ 65 years and that there was no notable increase of the rate of treatment discontinuation. In our study, the rate of adverse events that resulted in treatment discontinuation in the older patients was lower in the SMV group than in the TVR group, but the difference was not statistically significant. However, considering the risk of higher frequency and severity of adverse events associated with TVR-based triple therapy, we recommend the use of SMV rather than TVR.

The IL28B SNP genotype had a limited impact on the SVR rate with triple therapy in treatment-experienced patients[24], and the strength of the association between the IL28B genotype and the treatment outcome was attenuated in the triple therapy compared to the dual therapy[23,25]. In the present study, the IL28B SNP genotype displayed a striking influence on the outcome of both TVR- and SMV-based triple therapy, especially in older patients. In the older patients carrying the IL28B TT-genotype, the rates of SVR were 92.9% and 100% in the TVR and SMV groups, respectively. In contrast, in the older patients carrying the IL28B TG or GG-genotype, the rates of SVR were significantly decreased to 60% and 64.7% in the TVR and SMV groups (P = 0.038 and P < 0.01), respectively. Although the substitutions in the core aa70 of the HCV genotype 1b were reported to be important predictors of the efficacy of dual therapy and triple therapy[26,27], our study revealed that the substitutions in the HCV core aa70 were not associated with the achievement of SVR (data not shown). This discrepancy may be explained by the differences in the study population, as our study consisted of a relatively higher number of aged patients. We also measured serum CXCL10 in patients treated with TVR-based triple therapy because previous studies have reported that pretreatment serum CXCL10 concentrations were associated with early virological response and treatment efficacy in patients treated with this therapy[28,29]. However, we did not confirm the utility of pretreatment CXCL10 concentrations as a predictor of virological response in patients treated with TVR-based triple therapy.

The present study has a number of limitations. First, the sample size might have provided inadequate statistical power to detect definitive differences between the SVR and no-SVR data in both the older and younger patients. However, the best of our knowledge, this is the first study to compare the efficacy and safety of TVR- and SMV-based triple therapies for elderly patients aged 66 years or older. Second, we only investigated Japanese patients with the HCV genotype 1b. Among the Japanese population, the favorable IL28B SNP is found in the majority of the population (approximately 75%)[4]. Therefore, our results may not be generalizable to other racial cohorts. Third, the older patients who enrolled in the study did not have any severe baseline complications, such as renal and hematological diseases. Therefore, the conclusions drawn regarding the safety of triple therapies may be limited. However, we believe that our selection of older patients for the triple therapies was appropriate and acceptable. Therefore, our findings regarding the absence of severe adverse events, even in the older patients, are important.

Treatment for CHC has been changing worldwide[30,31], and IFN-free DAA combination therapies are now available in Japan. Although the majority of CHC patients are usually treated with IFN-free DAA combination therapies, PegIFN and RBV-based therapy may still have utility in a small number of patients who do not show a favorable effect after the treatment with IFN-free DAA therapies. Moreover, considering the effect of preventing HCC by an eradication of HCV, long-term prevention of HCC has been shown only through the use of IFN-based therapies thus far[32,33]. Therefore, we believe that the present study will provide useful information regarding antiviral treatment for older patients with CHC.

In conclusion, we found that both TVR- and SMV-based triple therapies can be successfully used to treat patients aged 66 years or older with genotype 1b CHC. The IL28B genotype indicates a potential to achieve SVR in these difficult-to-treat older patients.

COMMENTS

Background

In Japan, an estimated 1.5-2 million people are infected with hepatitis C virus (HCV), and these patients are older than those infected in Europe and the United States. However, previous studies describing the safety and efficacy of telaprevir (TVR)- and simeprevir (SMV)-based triple therapies, especially in elderly patients with chronic HCV infections, are limited.

Research frontiers

The patients were categorized into two groups according to age as follows: a younger group of patients aged ≤ 65 years old and an older group of patients aged > 65 years old. The rate of sustained virological response (SVR) did not significantly differ between the younger and older patients in both the TVR and SMV groups. The rate of SVR did not significantly differ between the TVR and SMV group, although the rate of rapid virological response was significantly higher in the SMV group than the TVR group. The rate of adverse events resulted in treatment discontinuation did not differ between the younger and older patients in both TVR and SMV group, although a higher frequency and severity of adverse events has been reported in patients treated with TVR-based triple therapy compared to patients treated with pegylated interferon (PegIFN) and ribavirin (RBV) dual therapy.

Innovations and breakthroughs

In this study, the authors found that both TVR- and SMV-based triple therapies can be successfully used to treat patients aged 66 years or older with genotype 1b chronic hepatitis C (CHC). The interleukin 28B genotype indicates a potential to achieve SVR in these difficult-to-treat elderly patients.

Applications

Treatment for CHC has been changing worldwide, and interferon (IFN)-free direct-acting antiviral agents (DAA) combination therapies are now available in. Although the majority of CHC patients are usually treated with IFN-free DAA combination therapies, PegIFNα and RBV-based therapy may still have utility in a small number of patients who do not show a favorable effect after the treatment with IFN-free DAA therapies. Importantly, HCV mutants that are resistant to multiple IFN-free DAA therapies have been shown to be sensitive to IFN-based therapies. Moreover, considering the effect of preventing HCC by an eradication of HCV, long-term prevention of HCC has been shown only through the use of IFN-based therapies thus far. Therefore, they believe that the present study will still provide useful information regarding antiviral treatment for older patients with CHC.

Terminology

TVR: An HCV non-structural 3/4A (NS3/4A) protease inhibitor; SMV: A second-generation oral HCV NS3/4A protease inhibitor with antiviral activity against HCV genotype 1, 2, 4, 5, and 6 infections.

Peer-review

The manuscript is well written and it is clear.

REFERENCES

1 **Seeff LB**, Buskell-Bales Z, Wright EC, Durako SJ, Alter HJ, Iber FL, Hollinger FB, Gitnick G, Knodell RG, Perrillo RP. Long-term mortality after transfusion-associated non-A, non-B hepatitis. The National Heart, Lung, and Blood Institute Study Group. *N Engl J Med* 1992; **327**: 1906-1911 [PMID: 1454085 DOI: 10.1056/NEJM199212313272703]

2 **Mohd Hanafiah K**, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. *Hepatology* 2013; **57**: 1333-1342 [PMID: 23172780 DOI: 10.1002/hep.26141]

3 **Namiki I**, Nishiguchi S, Hino K, Suzuki F, Kumada H, Itoh Y, Asahina Y, Tamori A, Hiramatsu N, Hayashi N, Kudo M. Management of hepatitis C; Report of the Consensus Meeting at the 45th Annual Meeting of the Japan Society of Hepatology (2009). *Hepatol Res* 2010; **40**: 347-368 [PMID: 20394674]

4 **Furusyo N**, Ogawa E, Nakamuta M, Kajiwara E, Nomura H, Dohmen K, Takahashi K, Satoh T, Azuma K, Kawano A, Tanabe Y, Kotoh K, Shimoda S, Hayashi J. Telaprevir can be successfully and safely used to treat older patients with genotype 1b chronic hepatitis C. *J Hepatol* 2013; **59**: 205-212 [PMID: 23542346 DOI: 10.1016/j.jhep.2013.03.020]

5 **Asahina Y**, Tsuchiya K, Tamaki N, Hirayama I, Tanaka T, Sato M, Yasui Y, Hosokawa T, Ueda K, Kuzuya T, Nakanishi H, Itakura J, Takahashi Y, Kurosaki M, Enomoto N, Izumi N. Effect of aging on risk for hepatocellular carcinoma in chronic hepatitis C virus infection. *Hepatology* 2010; **52**: 518-527 [PMID: 20683951 DOI: 10.1002/hep.23691]

6 **Zeuzem S**. Heterogeneous virologic response rates to interferon-based therapy in patients with chronic hepatitis C: who responds less well? *Ann Intern Med* 2004; **140**: 370-381 [PMID: 14996679]

7 **Honda T**, Katano Y, Shimizu J, Ishizu Y, Doizaki M, Hayashi K, Ishigami M, Itoh A, Hirooka Y, Nakano I, Urano F, Yoshioka K, Toyoda H, Kumada T, Goto H. Efficacy of peginterferon-alpha-2b plus ribavirin in patients aged 65 years and older with chronic hepatitis C. *Liver Int* 2010; **30**: 527-537 [PMID: 19523048 DOI: 10.1111/j.1478-3231.2009.02064.x]

8 **Furusyo N**, Ogawa E, Sudoh M, Murata M, Ihara T, Hayashi T, Ikezaki H, Hiramine S, Mukae H, Toyoda K, Taniai H, Okada K, Kainuma M, Kajiwara E, Hayashi J. Raloxifene hydrochloride is an adjuvant antiviral treatment of postmenopausal women with chronic hepatitis C: a randomized trial. *J Hepatol* 2012; **57**: 1186-1192 [PMID: 22889955 DOI: 10.1016/j.jhep.2012.08.003]

9 **Reddy KR**, Zeuzem S, Zoulim F, Weiland O, Horban A, Stanciu C, Villamil FG, Andreone P, George J, Dammers E, Fu M, Kurland D, Lenz O, Ouwerkerk-Mahadevan S, Verbinnen T, Scott J, Jessner W. Simeprevir versus telaprevir with peginterferon and ribavirin in previous null or partial responders with chronic hepatitis C virus genotype 1 infection (ATTAIN): a randomised, double-blind, non-inferiority phase 3 trial. *Lancet Infect Dis* 2015; **15**: 27-35 [PMID: 25482330 DOI: 10.1016/S1473-3099(14)71002-3]

10 **Jacobson IM**, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, Marcellin P, Muir AJ, Ferenci P, Flisiak R, George J, Rizzetto M, Shouval D, Sola R, Terg RA, Yoshida EM, Adda N, Bengtsson L, Sankoh AJ, Kieffer TL, George S, Kauffman RS, Zeuzem S. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med* 2011; **364**: 2405-2416 [PMID: 21696307 DOI: 10.1056/NEJMoa1012912]

11 **Zeuzem S**, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, Focaccia R, Younossi Z, Foster GR, Horban A, Ferenci P, Nevens F, Müllhaupt B, Pockros P, Terg R, Shouval D, van Hoek B, Weiland O, Van Heeswijk R, De Meyer S, Luo D, Boogaerts G, Polo R, Picchio G, Beumont M. Telaprevir for retreatment of HCV infection. *N Engl J Med* 2011; **364**: 2417-2428 [PMID: 21696308 DOI: 10.1056/NEJMoa1013086]

12 **Fried MW**, Buti M, Dore GJ, Flisiak R, Ferenci P, Jacobson I, Marcellin P, Manns M, Nikitin I, Poordad F, Sherman M, Zeuzem S, Scott J, Gilles L, Lenz O, Peeters M, Sekar V, De Smedt G, Beumont-Mauviel M. Once-daily simeprevir (TMC435) with pegylated interferon and ribavirin in treatment-naïve genotype 1 hepatitis C: the randomized PILLAR study. *Hepatology* 2013; **58**: 1918-1929 [PMID: 23907700 DOI: 10.1002/hep.26641]

13 **Jacobson IM**, Dore GJ, Foster GR, Fried MW, Radu M, Rafalsky VV, Moroz L, Craxi A, Peeters M, Lenz O, Ouwerkerk-Mahadevan S, De La Rosa G, Kalmeijer R, Scott J, Sinha R, Beumont-Mauviel M. Simeprevir with pegylated interferon alfa 2a plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-1): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet* 2014; **384**: 403-413 [PMID: 24907225 DOI: 10.1016/S0140-6736(14)60494-3]

14 **Hayashi N**, Izumi N, Kumada H, Okanoue T, Tsubouchi H, Yatsuhashi H, Kato M, Ki R, Komada Y, Seto C, Goto S. Simeprevir with peginterferon/ribavirin for treatment-naïve hepatitis C genotype 1 patients in Japan: CONCERTO-1, a phase III trial. *J Hepatol* 2014; **61**: 219-227 [PMID: 24727123]

15 **Izumi N**, Hayashi N, Kumada H, Okanoue T, Tsubouchi H, Yatsuhashi H, Kato M, Ki R, Komada Y, Seto C, Goto S. Once-daily simeprevir with peginterferon and ribavirin for treatment-experienced HCV genotype 1-infected patients in Japan: the CONCERTO-2 and CONCERTO-3 studies. *J Gastroenterol* 2014; **49**: 941-953 [PMID: 24626851 DOI: 10.1007/s00535-014-0949-8]

16 **Kumada H**, Hayashi N, Izumi N, Okanoue T, Tsubouchi H, Yatsuhashi H, Kato M, Rito K, Komada Y, Seto C, Goto S. Simeprevir (TMC435) once daily with peginterferon-α-2b and ribavirin in patients with genotype 1 hepatitis C virus infection: The CONCERTO-4 study. *Hepatol Res* 2015; **45**: 501-513 [PMID: 24961662 DOI: 10.1111/hepr.12375]

17 **Bedossa P**, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. *Hepatology* 1996; **24**: 289-293 [PMID: 8690394 DOI: 10.1002/hep.510240201]

18 **Enomoto N**, Sakuma I, Asahina Y, Kurosaki M, Murakami T, Yamamoto C, Ogura Y, Izumi N, Marumo F, Sato C. Mutations in the nonstructural protein 5A gene and response to interferon in patients with chronic hepatitis C virus 1b infection. *N Engl J Med* 1996; **334**: 77-81 [PMID: 8531962 DOI: 10.1056/NEJM199601113340203]

19 **Akuta N**, Suzuki F, Sezaki H, Suzuki Y, Hosaka T, Someya T, Kobayashi M, Saitoh S, Watahiki S, Sato J, Matsuda M, Kobayashi M, Arase Y, Ikeda K, Kumada H. Association of amino acid substitution pattern in core protein of hepatitis C virus genotype 1b high viral load and non-virological response to interferon-ribavirin combination therapy. *Intervirology* 2005; **48**: 372-380 [PMID: 16024941 DOI: 10.1159/000086064]

20 **Hara T**, Akuta N, Suzuki F, Sezaki H, Suzuki Y, Hosaka T, Kobayashi M, Kobayashi M, Saitoh S, Kumada H. A pilot study of triple therapy with telaprevir, peginterferon and ribavirin for elderly patients with genotype 1 chronic hepatitis C. *J Med Virol* 2013; **85**: 1746-1753 [PMID: 23861088 DOI: 10.1002/jmv.23673]

21 **Ogawa E**, Furusyo N, Kajiwara E, Nomura H, Kawano A, Takahashi

K, Dohmen K, Satoh T, Azuma K, Nakamuta M, Koyanagi T, Kotoh K, Shimoda S, Hayashi J. Comparative effectiveness and safety study of triple therapy with simeprevir or telaprevir for non-cirrhotic patients with chronic hepatitis C virus genotype 1b infection. *J Gastroenterol Hepatol* 2015; **30**: 1759-1767 [PMID: 26095167 DOI: 10.1111/jgh.13016]
22 **Yoshizawa H**, Tanaka J, Miyakawa Y. National prevention of hepatocellular carcinoma in Japan based on epidemiology of hepatitis C virus infection in the general population. *Intervirology* 2006; **49**: 7-17 [PMID: 16166783]
23 **Abe H**, Tsubota A, Shimada N, Atsukawa M, Kato K, Takaguchi K, Asano T, Chuganji Y, Sakamoto C, Toyoda H, Kumada T, Ide T, Sata M, Aizawa Y. Predictors of response to 24-week telaprevir-based triple therapy for treatment-naïve genotype 1b chronic hepatitis C patients. *Gastroenterol Res Pract* 2014; **2014**: 549709 [PMID: 25197269 DOI: 10.1155/2014/549709]
24 **Pol S**, Aerssens J, Zeuzem S, Andreone P, Lawitz EJ, Roberts S, Younossi Z, Foster GR, Focaccia R, Horban A, Pockros PJ, Van Heeswijk RP, De Meyer S, Luo D, Botfield M, Beumont M, Picchio G. Limited impact of IL28B genotype on response rates in telaprevir-treated patients with prior treatment failure. *J Hepatol* 2013; **58**: 883-889 [PMID: 23321318 DOI: 10.1016/j.jhep.2012.12.023]
25 **Holmes JA**, Desmond PV, Thompson AJ. Does IL28B genotyping still have a role in the era of direct-acting antiviral therapy for chronic hepatitis C infection? *J Viral Hepat* 2012; **19**: 677-684 [PMID: 22967098 DOI: 10.1111/jvh.12003]
26 **Akuta N**, Suzuki F, Hirakawa M, Kawamura Y, Sezaki H, Suzuki Y, Hosaka T, Kobayashi M, Kobayashi M, Saitoh S, Arase Y, Ikeda K, Chayama K, Nakamura Y, Kumada H. Amino acid substitution in HCV core/NS5A region and genetic variation near IL28B gene affect treatment efficacy to interferon plus ribavirin combination therapy. *Intervirology* 2012; **55**: 231-241 [PMID: 21734353 DOI: 10.1159/000328327]
27 **Akuta N**, Suzuki F, Hirakawa M, Kawamura Y, Yatsuji H, Sezaki H, Suzuki Y, Hosaka T, Kobayashi M, Kobayashi M, Saitoh S, Arase Y, Ikeda K, Chayama K, Nakamura Y, Kumada H. Amino acid substitution in hepatitis C virus core region and genetic variation near the interleukin 28B gene predict viral response to telaprevir with peginterferon and ribavirin. *Hepatology* 2010; **52**: 421-429 [PMID: 20648473 DOI: 10.1002/hep.23690]
28 **Matsuura K**, Watanabe T, Iijima S, Murakami S, Fujiwara K, Orito E, Iio E, Endo M, Kusakabe A, Shinkai N, Miyaki T, Nojiri S, Joh T, Tanaka Y. Serum interferon-gamma-inducible protein-10 concentrations and IL28B genotype associated with responses to pegylated interferon plus ribavirin with and without telaprevir for chronic hepatitis C. *Hepatol Res* 2014; **44**: 1208-1216 [PMID: 24372894 DOI: 10.1111/hepr.12294]
29 **Nishikawa H**, Enomoto H, Nasu A, Aizawa N, Saito M, Tamori A, Kawada N, Kimura T, Osaki Y, Nishiguchi S. Clinical significance of pretreatment serum interferon-gamma-inducible protein 10 concentrations in chronic hepatitis C patients treated with telaprevir-based triple therapy. *Hepatol Res* 2014; **44**: E397-E407 [PMID: 24628684 DOI: 10.1111/hepr.12326]
30 **Webster DP**, Klenerman P, Dusheiko GM. Hepatitis C. *Lancet* 2015; **385**: 1124-1135 [PMID: 25687730]
31 **Fujii H**, Nishimura T, Umemura A, Nishikawa T, Yamaguchi K, Moriguchi M, Sumida Y, Mitsuyoshi H, Yokomizo C, Tanaka S, Ishikawa H, Nishioji K, Kimura H, Takami S, Nagao Y, Takeuchi T, Shima T, Sawa Y, Minami M, Yasui K, Itoh Y. Comparison of peg-interferon, ribavirin plus telaprevir vs simeprevir by propensity score matching. *World J Hepatol* 2015; **7**: 2841-2848 [PMID: 26668696 DOI: 10.4254/wjh.v7.i28.2841]
32 **Cardoso AC**, Moucari R, Figueiredo-Mendes C, Ripault MP, Giuily N, Castelnau C, Boyer N, Asselah T, Martinot-Peignoux M, Maylin S, Carvalho-Filho RJ, Valla D, Bedossa P, Marcellin P. Impact of peginterferon and ribavirin therapy on hepatocellular carcinoma: incidence and survival in hepatitis C patients with advanced fibrosis. *J Hepatol* 2010; **52**: 652-657 [PMID: 20346533 DOI: 10.1016/j.jhep.2009.12.028]
33 **Ikeda K**, Saitoh S, Arase Y, Chayama K, Suzuki Y, Kobayashi M, Tsubota A, Nakamura I, Murashima N, Kumada H, Kawanishi M. Effect of interferon therapy on hepatocellular carcinogenesis in patients with chronic hepatitis type C: A long-term observation study of 1,643 patients using statistical bias correction with proportional hazard analysis. *Hepatology* 1999; **29**: 1124-1130 [PMID: 10094956]

P- Reviewer: Conti B, Kawakami Y, Larrubia JR, Liang XS
S- Editor: Kong JX **L- Editor**: A **E- Editor**: Li D

WJH World Journal of Hepatology

Submit a Manuscript: http://www.wjgnet.com/esps/

DOI: 10.4254/wjh.v9.i5.263

World J Hepatol 2017 February 18; 9(5): 263-269

ISSN 1948-5182 (online)

ORIGINAL ARTICLE

Observational Study

Malnutrition negatively impacts the quality of life of patients with cirrhosis: An observational study

Gabriela Rojas-Loureiro, Alfredo Servín-Caamaño, Elizabeth Pérez-Reyes, Luis Servín-Abad, Fátima Higuera-de la Tijera

Gabriela Rojas-Loureiro, Elizabeth Pérez-Reyes, Fátima Higuera-de la Tijera, Liver Clinic, Gastroenterology Department, Hospital General de México "Dr. Eduardo Liceaga", Mexico City 06720, Mexico

Alfredo Servín-Caamaño, Internal Medicine Department, Hospital General de México "Dr. Eduardo Liceaga", Mexico City 06720, Mexico

Luis Servín-Abad, Gastroenterologist at Lakeland Regional Medical Center, Lakeland, FL 33803, United States

Author contributions: Higuera-de la Tijera F was the guarantor and designed the study; Rojas-Loureiro G, Servín-Caamaño A and Pérez-Reyes E participated in the acquisition, analysis and interpretation of data; Higuera-de la Tijera F wrote the manuscript; Servín-Abad L reviewed the final manuscript and revised the article critically for important intellectual content; all authors read and approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by The Coordination of Research from Gastroenterology Department from Hospital General de México.

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

Conflict-of-interest statement: The authors involved in this manuscript [Gabriela Rojas-Loureiro, Alfredo Servín-Caamaño, Elizabeth Pérez-Reyes, Luis Servín-Abad, Fátima Higuera-de la Tijera] have no conflicting commercial, personal, political, intellectual or religious interests.

Data sharing statement: No additional data are available.

Manuscript source: Invited manuscript

Correspondence to: Fátima Higuera-de la Tijera, MD, MSc, Liver Clinic, Gastroenterology Department, Hospital General de México "Dr. Eduardo Liceaga", Dr. Balmis 148, Mexico City 06726, Mexico. fatimahiguera@yahoo.com.mx
Telephone: +52-55-27892000-30047

Received: August 13, 2016
Peer-review started: August 14, 2016
First decision: September 2, 2016
Revised: October 28, 2016
Accepted: December 7, 2016
Article in press: December 9, 2016
Published online: February 18, 2017

Abstract

AIM

To verify how malnutrition is related to health-related quality of life (HRQL) impairment in patients with cirrhosis.

METHODS

Data was retrospectively abstracted from medical records and obtained by direct interview. We included patients with cirrhosis from any etiology, evaluated at the Liver Clinic from Gastroenterology Department in a tertiary healthcare center, from June 2014 to June 2016. Child-Pugh score, data about complications, and demographic, clinical and anthropometric characteristics of patients were obtained. Nutritional status was evaluated by the Subjective Global Assessment (SGA). HRQL was evaluated through the Chronic Liver Disease Questionnaire. Patients were requested to assess their global HRQL with the following code: 0 = impairment of HRQL, when it was compared with other healthy subjects; 1 = good HRQL, if it was similar to the quality of life of other healthy subjects. To compare the primary outcome between malnourished and well-nourished groups, the χ^2 test, Fisher's exact test or Student's *t*-test were used, based on the variable type. Associations between predictor variables and deterioration of HRQL were determined by calculating the hazard ratio and 95% confidence interval using Cox proportional hazards regression.

RESULTS

A total of 127 patients with cirrhosis were included, and the mean age was 54.1 ± 12.3 years-old. According to Child-Pugh scoring, 25 (19.7%) were classified as A (compensated), 76 (59.8%) as B, and 26 (20.5%) as C (B/C = decompensated). According to SGA, 58 (45.7%) patients were classified as well-nourished. Sixty-nine patients identified HRQL as good, and 76 patients (59.8%) perceived impairment of their HRQL. Multivariate analysis to determine associations between predictor variables and self-perception of an impairment of HRQL found strong association with malnutrition ($P < 0.0001$). The most important impaired characteristics in malnourished patients were: Presence of body pain, dyspnea on exertion with daily activities, decreased appetite, generalized weakness, trouble lifting or carrying heavy objects, and-decreased level of energy ($P < 0.0001$).

CONCLUSION

Malnutrition is a key factor related to impairment of HRQL in patients with cirrhosis.

Key words: Malnutrition; Subjective global assessment; Health-related quality of life; Cirrhosis; Chronic liver disease questionnaire

Core tip: Several factors, particularly the severity of disease, development of ascites, need for paracentesis and history of hospitalization for any cause, are factors that worsen the health-related quality of life (HRQL) of patients with cirrhosis. Noteworthy malnutrition is a very important factor which impacts negatively on HRQL of patients suffering cirrhosis; clinicians must recognize it promptly and search for strategies to avoid this preventable comorbidity.

Rojas-Loureiro G, Servín-Caamaño A, Pérez-Reyes E, Servín-Abad L, Higuera-de la Tijera F. Malnutrition negatively impacts the quality of life of patients with cirrhosis: An observational study. *World J Hepatol* 2017; 9(5): 263-269 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i5/263.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i5.263

INTRODUCTION

Cirrhosis and its complications are important factors which contribute to mortality worldwide[1]. Compared with healthy people, the patients with compensated cirrhosis have five times more risk of non-survival, and those with decompensated cirrhosis have ten times more risk of non-survival during follow-up[2].

Malnutrition is highly prevalent in cirrhotic patients. It is related to development of complications, or even death[3-5].

Despite new treatment options for viral hepatitis, the high frequency of undiagnosed patients with chronic viral hepatitis and the increased incidence of metabolic syndrome with non-alcoholic steatohepatitis had led to the number of individuals progressing to cirrhosis being expected to increase until about 2030[6]. Moreover, despite increased knowledge of the pathogenesis of cirrhosis and major advances in the treatment, there remains a paucity of information related to health-related quality of life (HRQL) in these patients. Furthermore, the emotional impact of cirrhosis on individual's lives is rarely considered in clinical practice[7].

HRQL is defined as the impact on three health domains regarding the patient's perception of their wellbeing: Physical, psychological, and social health. Measurement of HRQL requires administration of self-reported questionnaires[8,9].

The Chronic Liver Disease Questionnaire (CLDQ) assesses HRQL in patients with chronic liver disease across diagnoses, at all stages of disease and treatment. The CLDQ is a 29-item self-reported questionnaire, with patient response options extending from 1 to 7 (all to none of the time). The CLDQ addresses the following domains that when combined give a composite score that indicates overall HRQL: Fatigue, activity, emotional function, abdominal pain, systemic symptoms, and anxiety. Mean domain scores and an overall quality of life score can be calculated, with higher scores representing better outcome[9,10]. Previous studies have confirmed how HRQL deteriorates from compensated to decompensated cirrhosis[11].

Our aim in this study was to verify how malnutrition is related to HRQL impairment in patients with cirrhosis.

MATERIALS AND METHODS

Study design

We designed an observational analytic study. Data were retrospectively abstracted from medical records and obtained by direct interview. All study participants provided verbal informed consent prior to study enrollment.

Patients

We included patients with cirrhosis from any etiology, who were evaluated at the Liver Clinic from Gastroenterology Department in a tertiary healthcare center,

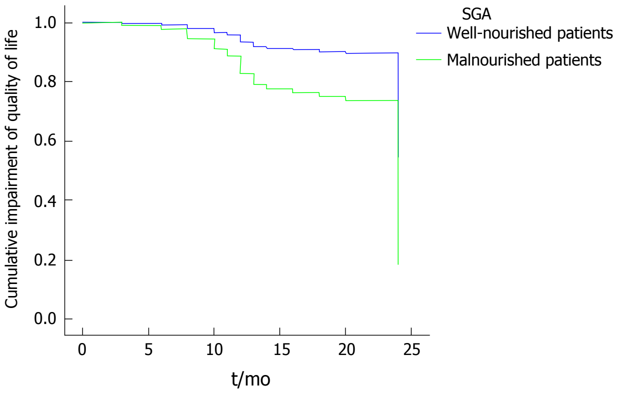

Figure 1 Kaplan- Meier curves showing the impairment of quality of life through the course of chronic liver disease, in patients with cirrhosis and malnutrition according to subjective global assessment. Malnourished patients had a worse quality of life during the follow-up in each visit to the physician, compared with those well-nourished patients. $P < 0.0001$. SGA: Subjective global assessment.

from June 2014 to June 2016. The Child-Pugh score was used to define compensated cirrhosis (Child-Pugh A) and decompensated cirrhosis (Child-Pugh B/C). We also collected data about complications of cirrhosis, including: Ascites, need of paracentesis, variceal bleeding, hepatic encephalopathy, and bacterial infection needing hospitalization. Patients with other chronic comorbidities, such as diabetes, chronic renal failure, heart or lung disease, neoplasms and acquired immunodeficiency syndrome, were excluded. We collected demographic, clinical and anthropometric characteristics of patients.

Anthropometric parameters

Weight, height, mid-arm circumference and triceps skinfold thickness were measured[12]. Body mass index (BMI) and ideal mid-arm muscle circumference were also calculated[13,14].

Nutritional status

Nutritional status was evaluated by the Subjective Global Assessment (SGA)[4,5,15]. Patients were catalogued as well nourished, or moderately or severely malnourished. We chose the SGA for this study because of its being a simple bedside method recommended by the experts when other more accurate methods, such as phase angle or body cell mass measured by bioelectric impedance analysis, are not available to assess nutritional status.

HRQL

HRQL was evaluated through the CLDQ[10]. In addition, patients were requested to assess their global HRQL with the following coding system: 0 = impairment of HRQL, when it was compared with other healthy subjects; 1 = good HRQL, if it was similar to the quality of life of other healthy subjects.

Statistical analysis

Numeric variables were stated as mean and standard deviation (SD); categorical variables were stated as proportions and percentages. To compare the primary outcome between malnourished and well-nourished groups, the χ^2 test, Fisher's exact test or Student's *t*-test were used, as appropriate. Associations between predictor variables and deterioration of quality of life were determined by calculating the hazard ratio (HR) and 95% confidence interval (CI) using Cox proportional hazards regression. The significant variables ($P < 0.05$) in the univariate model were included in the multivariate model. Kaplan-Meier curves were constructed to compare quality of life between well-nourished and malnourished patients, and for this purpose, we identified the time when patients were diagnosed with cirrhosis and the estimated time when patients noticed impairment of their quality of life. Statistical significance was considered as a *P*-value < 0.05.

RESULTS

A total of 127 patients with cirrhosis were included, 70 of which were female (55.1%) and 57 were male (44.9%); the mean age was 54.1 ± 12.3 years-old. Regarding the etiology of the cirrhosis, 68 patients (53.3%) had alcoholic cirrhosis, 23 (18.1%) had chronic hepatitis C, 21 (16.5%) had cryptogenic etiology, 11 (8.7%) had autoimmune hepatitis, 3 (2.4%) had non-alcoholic steato-hepatitis, and 1 (0.8%) had chronic hepatitis B. According to Child-Pugh scoring, 25 patients (19.7%) were classified as A (compensated), 76 (59.8%) as B, and 26 (20.5%) as C (B/C = decompensated). As determined by the SGA, 58 patients (45.7%) were well-nourished and 69 (54.3%) had some degree of malnutrition, including 66 (52%) with mild to moderate malnutrition and 3 (2.3%) with severe malnutrition. A total of 51 patients (40.2%) assessed their HRQL as good quality of life or similar to other healthy subjects; on the other hand, 76 patients (59.8%) perceived impairment of their HRQL in comparison with other healthy subjects. Characteristics of patients according to their self-perception of HRQL are shown and compared in Table 1. In the univariate analysis, decompensated cirrhosis, presence of ascites, need for paracentesis, hospitalization for any cause, and malnutrition were factors significantly associated with poor HRQL.

Multivariate analysis to determine associations between predictor variables and self-perception of an impairment of HRQL is shown in Table 2. The most important factor related to poor HRQL was malnutrition ($P < 0.0001$). Also, patients with malnutrition had poorer HRQL through the time course of their chronic liver disease, when compared with the well-nourished patients ($P < 0.0001$) (Figure 1).

Finally, the comparison of characteristics evaluated through CLDQ between malnourished and well-nourished patients is shown in Table 3. The most important impaired characteristics in malnourished patients were: Presence of body pain, dyspnea on exertion with daily activities, decreased appetite, generalized weakness, trouble lifting or carrying heavy objects, and decreased

Table 1 Comparison between the patient characteristics according to the self-perception of quality of life

Characteristic	Good quality of life (n = 51)	Impairment of quality of life (n = 76)	P
Male	24 (47.1)	33 (43.4)	0.69
Age (yr)	54.8 ± 10.3	53.7 ± 13.5	0.61
Decompensated or Child B/C	30 (58.8)	63 (82.9)	0.003
Etiology			
Alcohol	28 (55.0)	40 (52.7)	0.83
Viral	9 (17.6)	15 (19.7)	
NASH	2 (3.9)	1 (1.3)	
Cryptogenic	8 (15.7)	13 (17.1)	
Autoimmune	4 (7.8)	7 (9.2)	
Weight in kg	65.2 ± 14.9	63.7 ± 13.4	0.55
Body mass index (kg/m^2)	26.6 ± 5.2	26.8 ± 4.0	0.32
Triceps skinfold thickness (cm)	1.4 ± 0.7	1.4 ± 0.8	0.79
Mid-arm circumference (cm)	26.4 ± 4.7	23.9 ± 3.7	0.001
Ideal mid-arm muscle circumference (cm)	22.1 ± 4.1	19.6 ± 2.8	< 0.0001
Malnourished according to SGA	14 (27.5)	55 (72.4)	< 0.0001
Presence of ascites	19 (37.3)	48 (63.2)	0.004
Need for paracentesis	7 (13.7)	25 (32.9)	0.02
Development of variceal bleeding	12 (23.5)	18 (23.7)	0.98
Development of hepatic encephalopathy	19 (37.3)	30 (39.5)	0.80
Bacterial infection requiring hospitalization	6 (11.8)	14 (18.4)	0.45
Any complication requiring hospitalization	32 (62.7)	62 (81.6)	0.02

Categorical variables are expressed as n (%), and compared by χ^2 or Fisher's exact test. Numeric variables are expressed as median and SD, and compared by Student's t-test. Statistical significance was considered as a P-value of < 0.05. NASH: Non-alcoholic steatohepatitis; SGA: Subjective global assessment.

Table 2 Multivariate analysis to identify factors associated with self-perception of impairment of quality of life

Characteristic	HR (95%CI)	P
Malnourished according to SGA	2.8 (1.6-5.0)	< 0.0001
Need for paracentesis	1.8 (1.0-3.2)	0.05
Presence of ascites	1.4 (0.7-2.7)	0.38
Any complication requiring hospitalization	1.1 (0.5-2.6)	0.82
Decompensated or Child B/C	1.8 (0.0-4.0)	0.14

Cox regression, statistical significance was considered as a P-value of < 0.05. HR: Hazard ratio; SGA: Subjective global assessment.

level of energy (P < 0.0001).

DISCUSSION

Cirrhosis represents the final stage of all chronic liver diseases. In its decompensated form, cirrhosis can result in portal hypertension and hepatic dysfunction. Cirrhosis is a leading cause of morbidity and mortality worldwide, and not only is related to decreased survival but also to poor HRQL[16].

Quality of life is a concept that reflects the positive and negative aspects of an individual's life. The term "HRQL" specifically addresses the impact of health on patients' wellbeing[9]. There are many factors that influence outcome and HRQL in patients with cirrhosis, however liver function clearly plays a major role affecting the HRQL of patients with cirrhosis. Patients with decompensated cirrhosis have an important impairment on HRQL[17]. Also, many symptoms can negatively impact HRQL in patients with cirrhosis; these symptoms can include abdominal bloating, nausea, somnolence, weight loss, weakness, fatigue and itching. All of these may interfere with patient's work, schooling, social activities, and sense of wellbeing[18].

In our study, we found that decompensated cirrhosis (Child B/C) is a factor related to impairment of HRQL; this finding is similar to other studies. Marchesini *et al*[19] also reported that the severity of liver disease or the development of complications were conditions clearly related to deterioration of perception of health. Similarly, we found that the presence of ascites and need for paracentesis were associated factors related to poor quality of life. Furthermore, hospitalization for any cause was a condition related to poor HRQL in patients with cirrhosis.

In our study, interestingly we found that patients with cirrhosis and malnutrition had a poorer HRQL when compared with well-nourished patients with cirrhosis. Furthermore, malnutrition was the main factor contributing to impairment of HRQL in these patients. Cirrhosis is also associated with malnutrition, which is a complication that negatively affects cirrhotic patients, particularly those decompensated[20-23]. In patients with cirrhosis, the prevalence of malnutrition has been reported between 20% to 60%[24-27]. In a previous study conducted by Pérez-Reyes *et al*[4] in a Hispanic population, the prevalence of malnutrition was as high as 56.3%. In the present study, we also found a high frequency of malnutrition in patients with cirrhosis (54.3%). Malnutrition in cirrhosis is related to development of ascites, encephalopathy, spontaneous bacterial peritonitis, other bacterial infections and hepatorenal syndrome[4,28-32]. But also, malnutrition deteriorates the HRQL in patients with cirrhosis[33-35] and several other gastrointestinal and non-gastrointestinal diseases[36,37]. Our study confirms that malnutrition is

Table 3 Chronic Liver Diseases Questionnaire items comparison according to nutritional status

CLDQ item	Well-nourished (n = 58)	Malnourished (n = 69)	P
1 How much of the time during the last 2 wk have you been troubled by a feeling of abdominal bloating?	5.72 ± 1.531	4.67 ± 2.056	0.001
2 How much of the time have you been tired or fatigued during the last 2 wk?	3.69 ± 1.366	2.94 ± 1.259	0.002
3 How much of the time during the last 2 wk have you experienced body pain?	4.14 ± 0.868	3.57 ± 0.848	0.0001
4 How often during the last 2 wk have you felt sleepy during the day?	5.05 ± 1.343	4.55 ± 1.105	0.02
5 How much of the time during the last 2 wk have you experienced abdominal pain?	5.45 ± 1.273	4.96 ± 1.529	0.05
6 How much of the time during the last 2 wk have you experienced dyspnea on exertion, being a problem for you in your daily activities?	6.16 ± 0.951	5.33 ± 1.431	0.0001
7 How much of the time during the last 2 wk have you not been able to eat as much as you would like?	6.12 ± 1.010	3.55 ± 1.549	0.0001
8 How much of the time in the last 2 wk have you been bothered by having decreased strength?	4.91 ± 1.218	2.90 ± 1.447	0.0001
9 How often during the last 2 wk have you had trouble lifting or carrying heavy objects?	5.62 ± 0.834	4.09 ± 1.391	0.0001
10 How often during the last 2 wk have you felt anxious?	5.52 ± 1.112	5.33 ± 1.379	0.41
11 How often during the last 2 wk have you felt a decreased level of energy?	5.19 +1.100	3.20 ± 1.491	0.0001
12 How much of the time during the last 2 wk have you felt unhappy?	5.12 ± 1.077	4.41 ± 1.527	0.003
13 How often during the last 2 wk have you felt drowsy?	4.97 ± 1.324	4.55 ± 1.051	0.05
14 How much of the time during the last 2 wk have you been bothered by a limitation of your diet?	4.14 ± 1.206	3.91 ± 1.160	0.29
15 How often during the last 2 wk have you been irritable?	5.52 ± 1.128	5.36 ± 1.175	0.45
16 How much of the time during the last 2 wk have you had difficulty sleeping at night?	5.02 ± 1.493	4.87 ± 1.444	0.57
17 How much of the time during the last 2 wk have you been troubled by a feeling of abdominal discomfort?	5.62 ± 1.437	4.77 ± 1.816	0.004
18 How much of the time during the last 2 wk have you been worried about the impact your liver disease has on your family?	5.84 ± 1.056	5.94 ± 1.371	0.66
19 How much of the time during the last 2 wk have you had mood swings?	5.50 ± 1.417	5.83 ± 1.283	0.18
20 How much of the time during the last 2 wk have you been unable to fall asleep at night?	5.10 ± 1.360	4.67 ± 1.569	0.99
21 How often during the last 2 wk have you had muscle cramps?	5.52 ± 1.047	5.39 ± 1.074	0.51
22 How much of the time during the last 2 wk have you been worried that your symptoms will develop into major problems?	4.19 + 1.515	4.45 ± 1.586	0.35
23 How much of the time during the last 2 wk have you had a dry mouth?	5.40 ± 1.184	5.30 ± 1.192	0.66
24 How much of the time during the last 2 wk have you felt depressed?	5.33 ± 1.082	4.68 ± 1.745	0.01
25 How much of the time during the last 2 wk have you been worried about your condition getting worse?	4.05 ± 1.191	4.28 ± 1.454	0.34
26 How much of the time during the last 2 wk have you had problems concentrating?	5.34 ± 1.132	4.74 ± 1.569	0.01
27 How much of the time have you been troubled by itching during the last 2 wk?	5.71 ± 1.451	6.20 ± 1.065	0.03
28 How much of the time during the last 2 wk have you been worried about never feeling any better?	4.07 ± 1.153	4.36 ± 1.382	0.20
29 How much of the time during the last 2 wk have you been concerned about the availability of a liver if you need a liver transplant?	4.22 ± 1.312	4.23 ± 1.467	0.97

Data are expressed as median and SD, and compared with Student's t-test. Statistical significance was considered as a P-value of < 0.05. CLDQ: Chronic Liver Diseases Questionnaire.

a key factor related to impairment of HRQL in patients with cirrhosis, even when we adjusted for advanced liver disease or decompensation status, and for other major complications such as ascites, need for paracentesis and need for hospitalization for any cause.

In conclusion, cirrhosis is the end-stage of all chronic liver diseases; it contributes importantly to morbidity and mortality worldwide but also has a negative impact on HRQL that must be considered. Several factors contribute to a poor HRQL in patients with cirrhosis, however malnutrition, which is a highly prevalent comorbidity in patients with cirrhosis, represents a key factor related to poor HRQL in these patients. There is a need for developing strategies to evaluate more accurately patients with cirrhosis and to identify promptly those patients at risk of malnutrition.

COMMENTS

Background

Cirrhosis is a significant contributor to global mortality. Prevalence of malnutrition is high in patients with cirrhosis and is related to increased complications or even death. Despite increased knowledge of the pathogenesis of cirrhosis, there remains a paucity of information related to health-related quality of life (HRQL) in these patients.

Research frontiers

The emotional impact of cirrhosis on individual's lives is rarely considered in clinical practice. The Chronic Liver Disease Questionnaire assesses HRQL in patients with chronic liver disease across diagnoses, at all stages of disease and treatment.

Innovations and breakthroughs

Cirrhosis is a leading cause of morbidity and mortality worldwide, and not only is related to decreased survival but also to poor quality of life. The term "HRQL" addresses the impact of health on a patient's wellbeing. Many factors influence HRQL in patients with cirrhosis, however the impact of comorbidities, such as malnutrition, are not well understood. The authors found that patients with cirrhosis and malnutrition had worse quality of life when compared with well-nourished patients with cirrhosis. In this study, malnutrition was the main factor contributing to impairment of quality of life in these patients.

Applications

In this study, the authors found that several factors contribute to a poor health-related quality of life in patients with cirrhosis, however malnutrition, which is a highly prevalent comorbidity in these patients, represents a key factor related to poor quality of life in these patients. There is a need for developing strategies to evaluate more accurately patients with cirrhosis and to identify promptly those patients at risk of malnutrition.

Terminology

Nutritional status was defined through the Subjective Global Assessment and patients were divided as follows: Well-nourished, or moderately or severely malnourished. The HRQL is defined as the impact on three health domains-physical, psychological, and social health-on patient perception of their wellbeing.

Peer-review

Very nice and well written paper.

REFERENCES

1 **Tucker ME.** Global burden of liver disease substantial. Available from: URL: http://www.medscape.com/viewarticle/813788#1
2 **Fleming KM**, Aithal GP, Card TR, West J. All-cause mortality in people with cirrhosis compared with the general population: a population-based cohort study. *Liver Int* 2012; **32**: 79-84 [PMID: 21745279 DOI: 10.1111/j.1478-3231.2011.02517]
3 **Maharshi S**, Sharma BC, Srivastava S. Malnutrition in cirrhosis increases morbidity and mortality. *J Gastroenterol Hepatol* 2015; **30**: 1507-1513 [PMID: 25974421 DOI: 10.1111/jgh.12999]
4 **Pérez-Reyes E,** Rivera-Sánchez J, Servín-Caamaño AI, Pérez-Torres E, Abdo-Francis JM, Higuera-de la Tijera F. Malnutrition is related to a higher frequency of serious complications in patients with cirrosis. *Rev Med Hosp Gen Méx* 2016; **79**: 11-16 [DOI: 10.1016/j.hgmx.2015.04.003]
5 **Landa-Galván HV**, Milke-García MP, León-Oviedo C, Gutiérrez-Reyes G, Higuera-de la Tijera F, Pérez-Hernández JL, Serralde-Zúñiga AE. [Nutritional assessment of alcoholic liver cirrhotic patients treated in the liver Clinic of the Mexico's General Hospital]. *Nutr Hosp* 2012; **27**: 2006-2014 [PMID: 23588452 DOI: 10.3305/nh.2012.27.6.6070]
6 **Davis GL**, Albright JE, Cook SF, Rosenberg DM. Projecting future complications of chronic hepatitis C in the United States. *Liver Transpl* 2003; **9**: 331-338 [PMID: 12682882 DOI: 10.1053/jlts.2003.50073]
7 **Anthony PP**, Ishak KG, Nayak NC, Poulsen HE, Scheuer PJ, Sobin LH. The morphology of cirrhosis. Recommendations on definition, nomenclature, and classification by a working group sponsored by the World Health Organization. *J Clin Pathol* 1978; **31**: 395-414 [PMID: 649765]
8 **Les I**, Doval E, Flavià M, Jacas C, Cárdenas G, Esteban R, Guardia J, Córdoba J. Quality of life in cirrhosis is related to potentially treatable factors. *Eur J Gastroenterol Hepatol* 2010; **22**: 221-227 [PMID: 19794311 DOI: 10.1097/MEG.0b013e3283319975]
9 **Loria A**, Escheik C, Gerber NL, Younossi ZM. Quality of life in cirrhosis. *Curr Gastroenterol Rep* 2013; **15**: 301 [PMID: 23250701]
10 **Younossi ZM**, Guyatt G, Kiwi M, Boparai N, King D. Development of a disease specific questionnaire to measure health related quality of life in patients with chronic liver disease. *Gut* 1999; **45**: 295-300 [PMID: 10403745]
11 **Younossi ZM**, Boparai N, McCormick M, Price LL, Guyatt G. Assessment of utilities and health-related quality of life in patients with chronic liver disease. *Am J Gastroenterol* 2001; **96**: 579-583 [PMID: 11232711 DOI: 10.1111/j.1572-0241.2001.03537.x]
12 **Lohman TG,** Roche AF, Martorell R. Anthropometric standardization reference manual. Champaign, IL: Human Kinetic Books; 1988
13 **Ratib S**, Fleming KM, Crooks CJ, Walker AJ, West J. Causes of death in people with liver cirrhosis in England compared with the general population: a population-based cohort study. *Am J Gastroenterol* 2015; **110**: 1149-1158 [PMID: 26169512 DOI: 10.1038/ajg.2015.191]
14 **Frisancho AR**. New norms of upper limb fat and muscle areas for assessment of nutritional status. *Am J Clin Nutr* 1981; **34**: 2540-2545 [PMID: 6975564]
15 **Morgan MY**, Madden AM, Soulsby CT, Morris RW. Derivation and validation of a new global method for assessing nutritional status in patients with cirrhosis. *Hepatology* 2006; **44**: 823-835 [PMID: 17006918 DOI: 10.1002/hep.21358]
16 **Nusrat S**, Khan MS, Fazili J, Madhoun MF. Cirrhosis and its complications: evidence based treatment. *World J Gastroenterol* 2014; **20**: 5442-5460 [PMID: 24833875 DOI: 10.3748/wjg.v20.i18.5442]
17 **Heidelbaugh JJ**, Bruderly M. Cirrhosis and chronic liver failure: part I. Diagnosis and evaluation. *Am Fam Physician* 2006; **74**: 756-762 [PMID: 16970019]
18 **Grattagliano I**, Ubaldi E, Bonfrate L, Portincasa P. Management of liver cirrhosis between primary care and specialists. *World J Gastroenterol* 2011; **17**: 2273-2282 [PMID: 21633593 DOI: 10.3748/wjg.v17.i18.2273]
19 **Marchesini G**, Bianchi G, Amodio P, Salerno F, Merli M, Panella C, Loguercio C, Apolone G, Niero M, Abbiati R; The Italian Study Group for Quality of Life in Cirrhosis. Factors associated with poor health-related quality of life of patients with cirrhosis. *Gastroenterology* 2001; **120**: 170-178 [PMID: 11208726 DOI: 10.1053/gast.2001.21193]
20 **Tessari P**. Protein metabolism in liver cirrhosis: from albumin to muscle myofibrils. *Curr Opin Clin Nutr Metab Care* 2003; **6**: 79-85 [PMID: 12496684 DOI: 10.1097/01.mco.0000049044.06038.30]
21 **Bianchi G**, Marzocchi R, Agostini F, Marchesini G. Update on nutritional supplementation with branched-chain amino acids. *Curr Opin Clin Nutr Metab Care* 2005; **8**: 83-87 [PMID: 15586005]
22 **Bilbao I**, Armadans L, Lazaro JL, Hidalgo E, Castells L, Margarit C. Predictive factors for early mortality following liver transplantation. *Clin Transplant* 2003; **17**: 401-411 [PMID: 14703921 DOI: 10.1034/j.1399-0012.2003.00068.x]
23 **Alvares-da-Silva MR**, Reverbel da Silveira T. Comparison between handgrip strength, subjective global assessment, and prognostic nutritional index in assessing malnutrition and predicting clinical outcome in cirrhotic outpatients. *Nutrition* 2005; **21**: 113-117 [PMID: 15723736 DOI: 10.1016/j.nut.2004.02.002]
24 **Peng S**, Plank LD, McCall JL, Gillanders LK, McIlroy K, Gane EJ. Body composition, muscle function, and energy expenditure in patients with liver cirrhosis: a comprehensive study. *Am J Clin Nutr* 2007; **85**: 1257-1266 [PMID: 17490961]
25 **Alberino F**, Gatta A, Amodio P, Merkel C, Di Pascoli L, Boffo G, Caregaro L. Nutrition and survival in patients with liver cirrhosis. *Nutrition* 2001; **17**: 445-450 [PMID: 11399401 DOI: 10.1016/S0899-9007(01)00521-4]
26 **Campillo B**, Richardet JP, Bories PN. Enteral nutrition in severely malnourished and anorectic cirrhotic patients in clinical practice. *Gastroenterol Clin Biol* 2005; **29**: 645-651 [PMID: 16141996]
27 **Plauth M**, Schütz ET. Cachexia in liver cirrhosis. *Int J Cardiol* 2002; **85**: 83-87 [PMID: 12163212 DOI: 10.1016/S0167-5273(02)00236-X]
28 **Kalaitzakis E**, Simrén M, Olsson R, Henfridsson P, Hugosson I, Bengtsson M, Björnsson E. Gastrointestinal symptoms in patients with liver cirrhosis: associations with nutritional status and health-related quality of life. *Scand J Gastroenterol* 2006; **41**: 1464-1472 [PMID: 17101578 DOI: 10.1080/00365520600825117]
29 **Kalaitzakis E**, Olsson R, Henfridsson P, Hugosson I, Bengtsson M, Jalan R, Björnsson E. Malnutrition and diabetes mellitus are related to hepatic encephalopathy in patients with liver cirrhosis. *Liver Int* 2007; **27**: 1194-1201 [PMID: 17919230 DOI: 10.1111/j.1478-3231.2007.01562.x]
30 **Huisman EJ**, Trip EJ, Siersema PD, van Hoek B, van Erpecum KJ. Protein energy malnutrition predicts complications in liver cirrhosis. *Eur J Gastroenterol Hepatol* 2011; **23**: 982-989 [PMID: 21971339 DOI: 10.1097/MEG.0b013e32834aa4bb]
31 **Merli M**, Lucidi C, Giannelli V, Giusto M, Riggio O, Falcone M, Ridola L, Attili AF, Venditti M. Cirrhotic patients are at risk for health care-associated bacterial infections. *Clin Gastroenterol Hepatol* 2010; **8**: 979-985 [PMID: 20621200 DOI: 10.1016/j.cgh.2010.06.024]
32 **Merli M**, Giusto M, Gentili F, Novelli G, Ferretti G, Riggio O, Corradini SG, Siciliano M, Farcomeni A, Attili AF, Berloco P, Rossi M. Nutritional status: its influence on the outcome of patients undergoing liver transplantation. *Liver Int* 2010; **30**: 208-214 [PMID: 19840246 DOI: 10.1111/j.1478-3231.2009.02135.x]

33 **Poupon RE**, Chrétien Y, Chazouillères O, Poupon R, Chwalow J. Quality of life in patients with primary biliary cirrhosis. *Hepatology* 2004; **40**: 489-494 [PMID: 15368455 DOI: 10.1002/hep.20276]
34 **Kalaitzakis E**. Gastrointestinal dysfunction in liver cirrhosis. *World J Gastroenterol* 2014; **20**: 14686-14695 [PMID: 25356031 DOI: 10.3748/wjg.v20.i40.14686]
35 **Shiraki M,** Nishiguchi S, Saito M, Fukuzawa Y, Mizuta T, Kaibori M, Hanai T, Nishimura K, Shimizu M, Tsurumi H, Moriwaki H. Nutritional status and quality of life in current patients with liver cirrhosis as assessed in 2007–2011. *Hepatol Res* 2013; **46:** 106-112 [DOI: 10.1111/hepr.12004]
36 **Norman K**, Kirchner H, Lochs H, Pirlich M. Malnutrition affects quality of life in gastroenterology patients. *World J Gastroenterol* 2006; **12**: 3380-3385 [PMID: 16733855 DOI: 10.3748/wjg.v12.i21.3385]
37 **Noman K,** Pichard C, Lochs H, Pirlich M. Prognostic impact of disease-related malnutrition. *Clin Nut* 2008; **27:** 5-15 [DOI: 10.1016/j.clnu.2007.10.007]

P- Reviewer: Ali A, Dina I, El-Karaksy HM, Facciorusso A, Gallo P, Sharma V
S- Editor: Song XX **L- Editor**: Filipodia **E- Editor**: Li D

World Journal of Hepatology

Submit a Manuscript: http://www.wjgnet.com/esps/

World J Hepatol 2017 February 18; 9(5): 270-277

DOI: 10.4254/wjh.v9.i5.270

ISSN 1948-5182 (online)

ORIGINAL ARTICLE

Observational Study

Addition of simvastatin to carvedilol non responders: A new pharmacological therapy for treatment of portal hypertension

Zeeshan Ahmad Wani, Sonmoon Mohapatra, Afaq Ahmad Khan, Ashutosh Mohapatra, Ghulam Nabi Yatoo

Zeeshan Ahmad Wani, Department of Gastroenterology and Hepatology, Institute of Liver and Biliary Sciences, New Delhi 110070, India

Sonmoon Mohapatra, Department of Internal Medicine, Rutgers Robert Wood Johnson Medical School/Saint Peters University Hospital, New Brunswick, NJ 08901, United States

Afaq Ahmad Khan, Department of Hematology and Oncology, JLNM hospital, Srinagar, Kashmir 190002, India

Ashutosh Mohapatra, Department of Gastroenterology and Hepatology, AMRI Hospitals, Bhubaneswar 751019, India

Ghulam Nabi Yatoo, Department of Gastroenterology and Hepatology, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Kashmir 190011, India

Author contributions: The work was carries out in collaboration of all authors; Wani ZA designed the study, performed the research and analyzed the data; Wani ZA and Mohapatra S wrote the first draft of the article; Khan AA and Yatoo GN made critical revisions related to important intellectual content of the manuscript; Mohapatra S and Mohapatra A edited and revised the manuscript for final submission.

Institutional review board statement: The study was reviewed and approved by Sher-i-Kashmir Institute of Medical Sciences Medical College, Srinagar, Jammu and Kashmir 190011, India and was conducted in Sher-i-Kashmir Institute of Medical Sciences Medical College, Srinagar and Noora Multispecialty Hospital, Srinagar, Kashmir, India.

Informed consent statement: All included patients gave their informed consent (written or verbal) prior to study inclusion.

Conflict-of-interest statement: The Authors have no conflict of interest.

Data sharing statement: No additional data are available.

Manuscript source: Unsolicited manuscript

Correspondence to: Sonmoon Mohapatra, MD, Department of Internal Medicine, Rutgers Robert Wood Johnson Medical School/Saint Peters University Hospital, 254 Easton Ave, New Brunswick, NJ 08901, United States. sonmoon0mohapatra@gmail.com
Telephone: +1-732-7458600

Received: November 13, 2016
Peer-review started: November 15, 2016
First decision: December 1, 2016
Revised: December 15, 2016
Accepted: January 11, 2017
Article in press: January 14, 2017
Published online: February 18, 2017

Abstract

AIM
To determine whether addition of simvastatin could be an important pharmacological rescue therapy for carvedilol non-responders.

METHODS
One hundred and two consecutive patients of cirrhosis of liver with significant portal hypertension were included. Hepatic venous pressure gradient (HVPG) was measured at the base line and after proper optimization of dose; chronic response was assessed at 3 mo. Carvedilol non-responders were given simvastatin 20 mg per day (increased to 40 mg per day at day 15). Carvedilol plus simvastatin was continued for 1 mo and hemodynamic response was again measured at 1 mo.

RESULTS
A total of 102 patients with mean age of 58.3 ± 6.6 years were included. Mean baseline HVPG was 16.75 ± 2.12 mmHg and after optimization of dose and reassessment of HVPG at 3 mo, mean reduction of HVPG from baseline was 5.5 ± 1.7 mmHg and 2.8 ± 1.6 mmHg among responders and non-responders respectively ($P < 0.001$). Addition of simvastatin to carvedilol non-responders resulted in significant response in 16 patients (42.1%) and thus overall response with carvedilol and carvedilol plus simvastatin was seen in 78 patients (80%). Two patients were removed in chronic protocol study with carvedilol and three patients were removed in carvedilol plus simvastatin study due to side effects.

CONCLUSION
Addition of simvastatin to carvedilol non-responders may prove to be an excellent rescue therapy in patients with portal hypertension.

Key words: Simvastatin; Cirrhosis; Carvedilol; Liver cirrhosis; Portal hypertension; Hepatocellular carcinoma

Core tip: There is no pharmacological option available for treatment of carvedilol nonresponders in patients with portal hypertension. Addition of simvastatin could be an important pharmacological rescue therapy for carvedilol nonresponders. This study showed that addition of simvastatin to carvedilol non responders can increase overall response to around 80%, which is one of the best possible pharmacologically produced chronic response and it opens a new strategy for portal hypertension treatment.

Wani ZA, Mohapatra S, Khan AA, Mohapatra A, Yatoo GN. Addition of simvastatin to carvedilol non responders: A new pharmacological therapy for treatment of portal hypertension. *World J Hepatol* 2017; 9(5): 270-277 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i5/270.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i5.270

INTRODUCTION

The prevalence of esophageal varices in an asymptomatic compensated patient is around 40%[1]. While the incidence of variceal development is roughly 6% per year, it doubles if hepatic venous pressure gradient (HVPG) rises above 10 mmHg. Thus, cirrhotics with HVPG of > 10 mmHg represent higher risk group. HVPG > 10 mmHg also correlates with higher risk of decompensation and hepatocellular carcinoma (HCC)[2,3]. The result of a number of meta-analysis has shown that, prognosis of cirrhotic patients improve with significant decrease in portal pressure, *i.e.*, when target decrease in HVPG (> 20% from baseline or to < 12 mmHg) is achieved[4,5]. In practice, cirrhotic patients complicated with varices should be treated except for Child-Pugh (C-P) class A patients with small varices without red color signs[6].

The role of non-selective beta blockers (NSBBs) and endoscopic variceal ligation (EVL) in the prevention of first variceal bleeding is conflicting. Analysis of a recent meta-analysis did not show any differences on mortality or bleeding rates between the two groups in trials with adequate bias control[7]. In contrast, another meta-analysis showed that compared with BBs, EVL reduced the risk of a first variceal bleed, although, there was no significant difference in survival[8]. Hence, the author concluded that EVL should be offered to patients with moderate to large oesphageal varices who are unlikely to comply or intolerant or who bleed while taking BB.

Still, the mainstream in pharmacological treatment of portal HTN (PHT) is NSBB like propranolol and nodolol which help in preventing first and recurrent variceal bleeding, gastropathy and spontaneous bacterial peritonitis (SBP)[9]. Drugs like isosorbide-5 mononitrate, prazosin or statins when added to NSBBs help in reducing the hepatic vascular tone and thus may turn many non-responders to responders[10,11]. Also, HVPG can be further decreased with these drugs. Recently our group has published a combined study on carvedilol in which 50% of the patients showed acute response and more than 60% of patients showed chronic response (please refer to definitions for details)[12]. We also showed in a separate study that, optimization of dose of carvedilol on chronic basis is an excellent policy for portal hypertension across different C-P class of liver disease[13].

Simvastatin improves liver generation of nitric oxide (NO) and hepatic endothelial dysfunction in patients with cirrhosis. Hence, it could be an effective therapy for portal hypertension. Recently, ideal drug for portal hypertension was pictured as one that should reduce portal pressure by decreasing intrahepatic vascular resistance while maintaining or enhancing hepatic blood flow[14,15]. Other desirable action would be an antifibrotic effect and a capacity to improve liver function. The drug that would be able to increase NO bioavailability in liver would fulfill many of the requirements[15-18]. However in patients with advanced cirrhosis, non-selective NO donors such as organic nitrates which enhance peripheral vasodilatation further decrease arterial pressure and activate endogenous vasoactive system. Thus, selectivity for hepatic circulation is a further requirement for vasodilators used to treat portal hypertension[19].

Recent experimental and human data[20,21] suggests that statins (3-hydroxy-3-methyl-COA reductase inhibitor) could decrease intra hepatic vascular resistance and improve flow mediated vasodilatation of liver vasculature in the cirrhotic liver. These effects are mediated by an up regulation of NO at the liver vasculature through an enhancement in endothelial NO synthetase activity[20]. Moreover, NO production in liver by statins is selective and could behave as true liver selective vasodilator.

Thus, the concept of our study was to assess the response of 3rd generation beta blocker carvedilol on

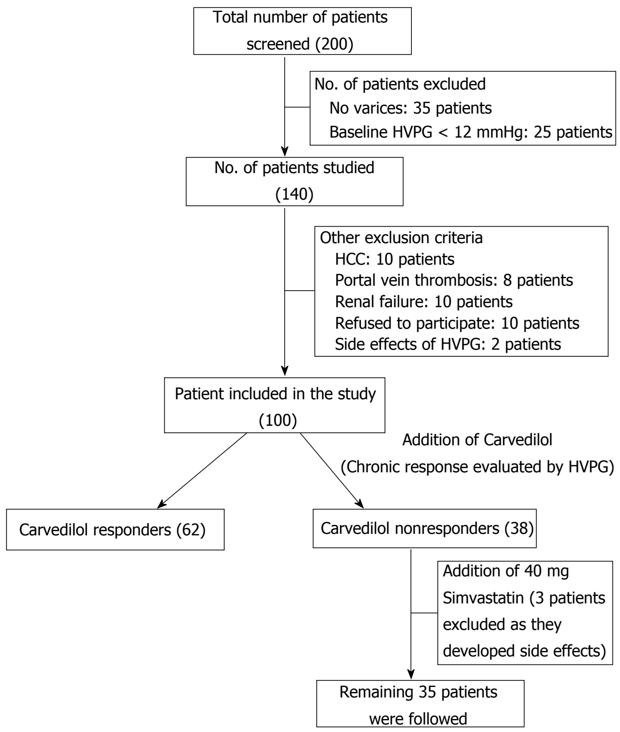

Figure 1 Study design. HVPG: Hepatic venous pressure gradient; HCC: Hepatocellular carcinoma.

chronic basis (after proper optimization of dose) and then to add simvastatin along with carvedilol, optimise dose in carvedilol non responders to have a new pharmacological approach and better rescue therapy.

MATERIALS AND METHODS

Patients and methods

We prospectively evaluated one hundred and two cirrhotic patients who were referred to our institution for hemodynamic evaluation from January, 2010 to December, 2014. The study was approved by the institutional review board (IRB) and all included patients gave informed consent for participation.

Diagnostic criteria for cirrhosis was based on clinical, biochemical, radiological and if needed on liver biopsy. The criteria for esophageal varices was based on quantitative grading used by Bavino consensus, *i.e.*, esophageal varices less than 5 mm are small varices and esophageal varices equal to or greater than 5 mm are considered large varices. Criteria used to diagnose ascites was according to international ascites club 2003, *i.e.*, grade Ⅰ - mild (ultrasound based), Grade Ⅱ - moderate, *i.e.*, (symmetrical abdominal distension) and Grade Ⅲ - gross with marked abdominal distension.

The inclusion criteria of the study include evidence of esophageal varices on upper gastrointestinal (GI) endoscopy, without a previous history of hemorrhage and a baseline HVPG of greater than 12 mmHg. Exclusion criteria were age < 18 years; severe liver failure INR > 2.5, or PT < 40% of control, bilirubin > 5 mg/dL; active alcohol consumption; Ⅳ drug abuse; renal failure, *i.e.*, creatinine > 1.5 mg/dL; HCC; contraindication to NSBB; pre or post hepatic cause of PHT; pregnancy; previous surgical shunt or TIPPS; treatment with calcium channel blockers; treatment with (3-hydroxy-3-methyl-COA reductase inhibitor) in past three months; a known hypersensitivity to simvastatin and refusal to participate in study.

Dosing Of NSBB

Baseline HVPG was measured for all included patients after 8 h of fasting. They were started on carvedilol 6.25 mg/d from the next day and dose was titrated by steps of 6.25 mg/wk. Dose of carvedilol was increased weekly until arterial systolic blood pressure (BP) was not less than < 90 mmHg and heart rate (HR) not less than < 55 bpm. Compliance with therapy was monitored by recording HR and BP during clinical visit.

Dosing of simvastatin

Carvedilol non-responders were added simvastatin 20 mg/d for 15 d (then increased to 40 mg). Complete clinical examination and blood tests were performed at day 15, patients were interrogated specifically for muscle weakness, if no safe end point was met, dose was increased to 40 mg/d and continuing with continuation of carvedilol. Treatment was maintained for 1 mo and then repeat hemodynamic response was measured.

Definitions

Acute response to carvedilol: Acute response to carvedilol is defined as "a drop in HVPG greater than 20% and or less than 12 mmHg from baseline at 90 min after administration of a single dose (12.5 mg) of carvedilol".

Chronic response to carvedilol: Chronic response to carvedilol is defined as "a drop in HVPG greater than 20% and or less than 12 mmHg from baseline at 3 mo after proper optimization of dose of carvedilol".

Response with addition of simvastatin

After 30 d of 40 mg simvastatin addition to carvedilol in carvedilol non responders, HVPG drop of greater than 20% from baseline and or less than 12 mmHg HVPG. The study design is illustrated in Figure 1. Dose optimization was done in all patients who were started with carvedilol. Once doses were optimized, weekly follow-up of each patient was done and HVPG was again measured at 3 mo of treatment. Patients were assessed for side effects; their BP and HR were measured on each follow-up visit. Carvedilol non responders were added with simvastatin 20 mg/d and after 15 d, all blood tests were taken for side effects of simvastatin and clinical history specifically muscle weakness was taken. With no clinical and biochemical evidence of adverse effects, patients were given 40 mg of simvastatin per day and continuing carvedilol for 1 mo, repeat hemodynamic assessment was done to see response in carvedilol non responders and thus overall response in the study group

Table 1 Baseline characteristics of 102 patients

Parameters	Description
Age (mean ± SD)	58.35 ± 6.62
Gender (male:female)	63:39
Child-Pugh class (A:B:C)	43:32:27
Etiology (Alcohol:Viral:NASH or Cryptogenic:AIH)	31:37:29:5
Oesophagea l Varices (small:large)	34:68
Ascites (No:Grade Ⅰ :Grade Ⅱ : Grade Ⅲ)	63:6:25:8
Total bilirubin (mg/dL)	1.96 ± 0.81
Serum albumin (mg/dL)	3.20 ± 0.49
Prothrombin time	14.13 ± 1.91
International normalized ratio	1.29 ± 0.16

NASH: Non-alcoholic steatohepatitis; AIH: Autoimmune hepatitis.

was seen.

Haemodynamic measurements

Under fluoroscopic guidance, hepatic vein catherization was performed according to the standards described by Bosch *et al*[22]. A 7F balloon tipped catheter was advanced to main right hepatic vein to measure wedged hepatic venous pressure gradient (WHPG). HVPG was measured as the difference between WHPG and free hepatic pressure gradient (FHPG). Swangaz catheter was advanced to pulmonary artery for measurement of cardio pulmonary pressures like pulmonary artery pressure (PAP), wedged pulmonary pressures (WPP), right arterial pressure (RAP), *etc*. All measurements were repeated three times and tracing were noted. Mean arterial pressure was measured non-invasively by automatic sphygmomanometer. HR was derived by continuous ECG monitoring and systemic vascular resistance (SVR) as (MAP - RAP/CO × 80).

Statistical analysis

The statistical methods of this study were reviewed by Dr. Khan from Noora Multispeciality Hospital, Srinagar, India. Statistical analysis was performed by using statistical package for social sciences (SPSS) version 22.0. Descriptive statistics was presented as proportion, Mean ± standard deviation (SD) and median with interquartile range. Comparative analysis was done by utilizing student's *t*-test and χ^2 test. The univariate and multivariate logistic regression was used for finding the predictors. A *P*-value less 0.05 was considered significant.

RESULTS

A total of 68 patients (66.7%) had large varices and 34 patients (33.3%) had small varices on upper GI endoscopy and 63 (61.8%) patients had no ascites while others had ascites. The baseline parameters are shown in Table 1.

After optimization of dose and reassessment of HVPG after 3 mo, total number of chronic responders was 62. However two patients discontinued treatment because of side effects. Mean duration of dose optimization was 15 ± 3 d. Mean reduction of HVPG from baseline and after 3 mo was 5.5 ± 1.7 mmHg and 2.8 ± 1.6 mmHg among responders and non-responders on chronic basis, respectively ($P < 0.001$). Mean dose of carvedilol was higher among non-responders (19.2 ± 5.7 mg) as compared to responders (18.7 ± 5.1 mg).

Effect of simvastatin addition to carvedilol non responders with continuation of carvedilol on reduction of portal hypertension and hemodynamic parameters

After assessing the chronic response at 3 mo with carvedilol, there were 38 patients who did not respond significantly to carvedilol and were thus called as carvedilol non-responder. In these 38 patients, simvastatin 20 mg/d was added initially for 15 d and at 15 d, side effects like muscle weakness along with biochemical parameters like CPK and ALT was seen. If CPK > 5 times and ALT > 3 times was found in any patient, they were withdrawn from the study. One patient developed CPK > 5 times with normal ALT was withdrawn from study on 15th day. Second patient developed hepatic encephalopathy and 3rd patient developed severe dizziness and both of these were withdrawn from study. Four patients developed minor side effects with normal CPK and ALT and were continued with treatment.

Among 38 carvedilol non responders, therefore, 35 patients continued carvedilol and simvastatin for 1 mo and then a repeat hemodynamic assessment was done. There were 16 responders and 19 non-responders at one month after adding simvastatin. Thus, overall carvedilol response in the study was 79.56% (78 patients). The pre baseline mean HVPG of carvedilol non responders was 16.429 mmHg which dropped to 13.029 mmHg, *i.e.*, 3.4 mmHg drop (> 20%) after adding simvastatin. The post carvedilol HVPG (post chronic) in carvedilol non responders was 14.457 mmHg which dropped to 13.029 mmHg, *i.e.*, 1.428 mmHg drop (9.87%) by adding simvastatin. It means that, simvastatin is responsible for HVPG drop of 9.87% in isolation.

Baseline and hemodynamic parameters of patients in whom simvastatin was added are shown in the Tables 2 and 3.

Gender, etiology, C-P class, ascites and variceal size were not seen to be statistically significant between responders and non-responders in simvastatin protocol. Among baseline hemodynamic parameters, only pre WHPG was significantly higher in responders as compared to non-responders ($P = 0.01$). HVPG was higher, though not statistically significant predictor of response. All hemodynamic parameters significantly decreased from baseline after treatment with simvastatin except FHVP which was significantly raised. All hemodynamic parameter were significantly decreased after treatment with simvastatin except FHVP which was significantly raised with respect to their values after chronic treatment with carvedilol (chronic protocol). Pre (baseline), post chronic (chronic carvedilol at 3 mo) and post simvastatin haemodynamic parameters in carvedilol non responders

Table 2 Baseline characteristics of 38 carvedilol non responders patients in whom Simvastatin was added

Parameters	Description
Age (mean ± SD)	58.45 ± 5.95
Gender (male:female)	21:17
Child-Pugh class (A:B:C)	14:13:11
Etiology (Alcohol:Viral:NASH or Cryptogenic)	12:15:11
OesophagealVarices (small:large)	12:26
Ascites (No:Grade 1:Grade 2:Grade 3)	21:4:8:5
Total bilirubin (mg/dL)	2.042 ± 0.77
Serum albumin (mg/dL)	3.203 ± 0.54
Prothrombin time	14.105 ± 2.16
International normalized ratio	1.318 ± 0.15

NASH: Non-alcoholic steatohepatitis.

Table 3 Hemodynamic parameters (mean) of studied population

Hemodynamic parameters	Baseline	Post chronic carvedilol (3 mo)	Post simvastatin
CO (L/min)	7.525 ± 0.19	6.38 ± 0.13	6.195 ± 0.17
HR (beats/min)	79.45 ± 2.50	57.45 ± 2.44	55.053 ± 1.67
MAP (mmHg)	89.53 ± 2.42	75.54 ± 1.97	74.500 ± 1.48
FHVP (mmHg)	8.28 ± 1.85	9.45 ± 1.90	10.086 ± 1.68
WHPG (mmHg)	25.08 ± 2.55	22.04 ± 2.56	23.114 ± 2.32
HVPG (mmHg)	16.75 ± 2.12	12.60 ± 2.24	13.029 ± 1.56

CO: Cardiac output; HR: Heart rate; MAP: Mean arterial pressure; FHVP: Free hepatic venous pressure; WHPG: Wedged hepatic venous pressure gradient; HVPG: Hepatic venous pressure gradient.

are shown as general linear model in Figure 2.

DISCUSSION

The mechanism of portal hypertension primarily involves an increase in resistance to portal outflow circulation. It leads to the formation of portosystemic collateral veins, of which esophageal varices have the highest clinical impact and the most severe complications. Other manifestations of portal hypertension include portal hypertensive gastropathy and large spontaneous shunts which refer to presence of patent paraumbilical vein, spleno-renal shunt, ano-rectosigmoid varices[23]. Recently, it has been showed that identifying cirrhotic patients with high blood ammonia concentrations could be clinically useful, as high levels would lead to suspicion of being in presence of collaterals[24]. The first line pharmacological therapy in portal hypertension is NSBB therapy. It decreases portal pressure through a reduction in portal venous inflow as a result of a decrease in cardiac output (β_1-adrenergic blockade) and splanchnic blood flow (β_2-adrenergic blockade). However, a major drawback of NSBBs is that not all patients respond to beta-blockers with a reduction of the HVPG.

Clinicians and researchers have always been looking for a more powerful portal hypotensive agent than propranolol and nodolol either administered alone or combination with nitrovasodilators. Advantages of medical therapy include safety and correction of detrimental systemic effects of portal hypertension. Our study tries to use best portal hypotensive agent, *i.e.*, 3rd generation beta blocker (non-selective) with mild vasodilating properties, *i.e.*, carvedilol which has been proven to show excellent hemodynamic response on chronic basis to the tune of 50%-72% of patients[25].

There are six studies which investigated chronic effects of carvedilol[26-28] with longest period of follow-up of 11 wk in one study. In another study by Stanley *et al*[27], seven of patients inclusively studied in acute protocol were unable to complete chronic administration of carvedilol as a result of side effects. This study suggests that, atleast for study group the administration of 25 mg without attempts to titrate according to response may not be ideal. Keeping in view the results of the above study, we used a titration or dose optimization based strategy for assessing chronic carvedilol response. It also studies difference of response between early liver disease and advanced liver disease, *i.e.*, between C-P class A and B/C on chronic basis. Further this study looks into maximum dose tolerated by different C-P class of liver disease on chronic basis apart from looking into predictor of chronic response. Idea of our study was to further move to add an agent to carvedilol non responders which has no effects on MAP or peripheral vascular resistance and which behaves like a true liver selective vasodilator, *i.e.*, simvastatin. Thus, it is the first study which has used a new pharmacological agent simvastatin in carvedilol non responders. Additive effects of simvastatin may markedly increase the number of patients who are protected effectively from portal hypertensive related complication. Such an effect is in agreement with liver perfusion studies in experimental model of cirrhosis which showed statins exert their hepatic vasodilating effect by upregulating endothelial NO production[29,30]. Our study shows that, chronic carvedilol non-responders were 62 (60%) which increased to overall response of nearly 80% once simvastatin was added to it. Thus around 42% of carvedilol non responders became responders by adding simvastatin.

In titration protocol on chronic basis, mean dose of carvedilol was 18.7 ± 5.1 mg and 19.7 ± 5.4 mg in responders and non-responders respectively. It was difficult to further increase the carvedilol dose in non-responders because of apprehension of hypotension and bradycardia. On multivariate analysis, absence of adverse events (OR = 11.3, 95%CI: 1.9-67.8) were the only independent predictors of chronic response (P < 0.05). Explanation for such results is that patients with less adverse events tolerated good dose to get good response. Major adverse events which resulted in drug discontinuation were hypotension in 2 patients and these patients could not be assessed further as shown in study design. Minor adverse events like fatigue, dyspnea, headache, temporary impotency, and dizziness were resolved without drug discontinuation. In addition, 2 patients had increase in ascites which resolved with escalation of diuretics. Further in our study, patients with

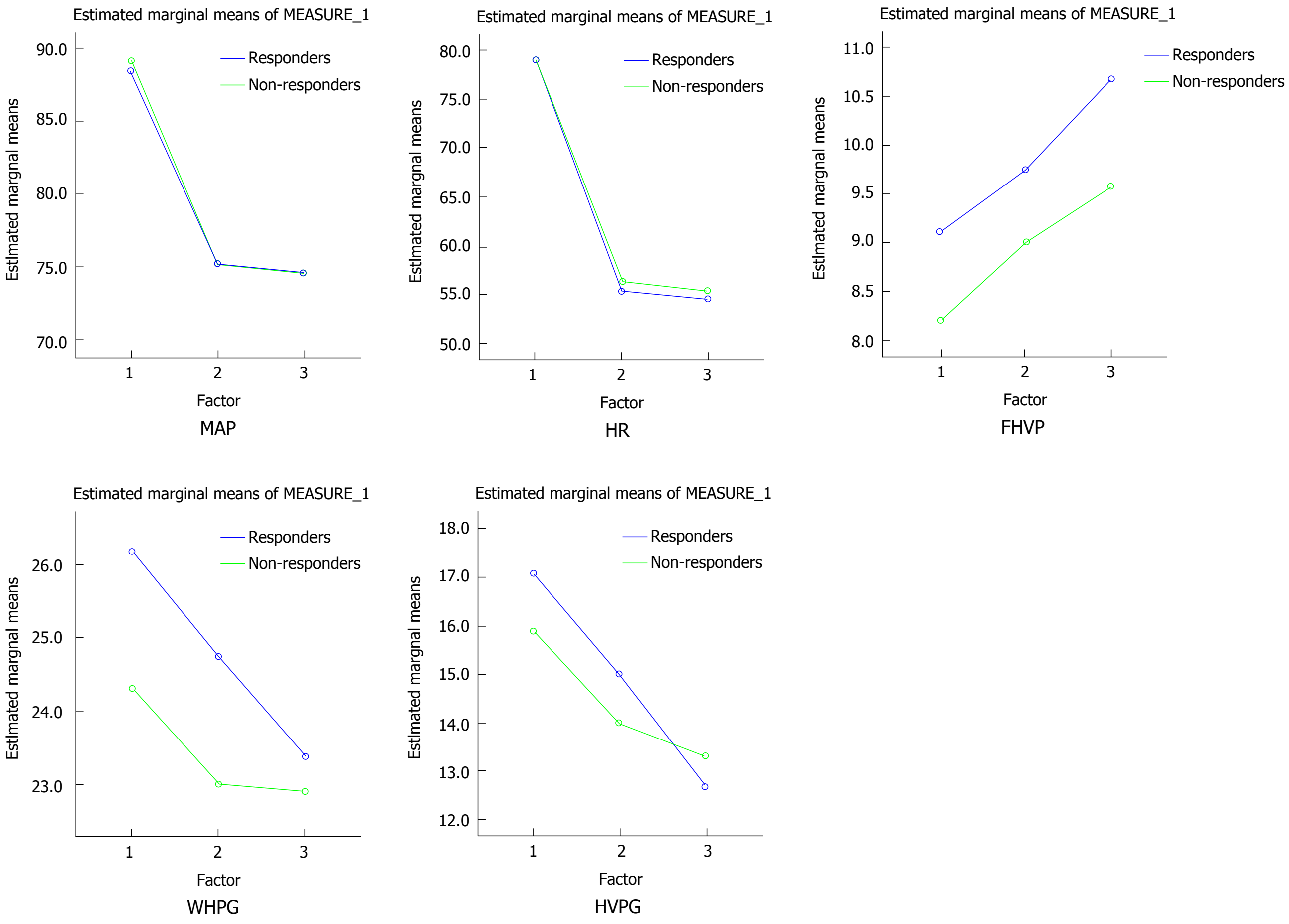

Figure 2 General linear model comparing Pre (baseline), chronic (carvedilol at 3 mo) and post simvastatin haemodynamic parameters with respect to time in carvedilol responders and non-responders. HR: Heart rate; MAP: Mean arterial pressure; FHVP: Free hepatic venous pressure; WHPG: Wedged hepatic venous pressure gradient; HVPG: Hepatic venous pressure gradient.

C-P class A cirrhosis has shown better chronic response as compared to C-P class B and C but it was not statically significant.

Our studies showed that addition of simvastatin to carvedilol non responders can increase overall response to around 80%, which is one of the best possible pharmacologically produced chronic response and it opens a new strategy for portal hypertension treatment.

Etiology, C-P class, gender, ascites, adverse events, variceal size was not seen statically significant predictors of response for simvastatin protocol. Pre WHPG (baseline WHPG) was seen significantly higher among responders than non-responders and all hemodynamic parameters significantly decreased from baseline after treatment with simvastatin except FHVP which significantly raised. Similar results were observed after chronic treatment with carvedilol. In our study, HVPG after adding simvastatin decreased mainly because of increase in FHVP. Previous studies have shown that patients with cirrhosis have blood pooling in splanchnic region that correlates with degree of portal hypertension[20]. This might suggest that decreases in hepatic resistance by simvastatin could reduce splanchnic congestion and improving central blood volume[21] and alternatively simvastatin may have normalized venous compliance and by this mechanism can inverse venacaval and right arterial pressure and thus increase FHVP.

It is well known that simvastatin improves hepatic clearance, intrinsic clearance, and hepatic extraction of indocyanine green, parameters that reflect effective liver perfusion. Thus, an increase in intrahepatic bioavailability of NO might result in improvement in amount of blood that has functional contact with hepatocytes that explains the improvement in quantitative tests of liver function after simvastatin. We have not done these tests of liver function in our study as it is already a proven fact[11,12].

An important concern with the use of statins in patients with cirrhosis is potential for inducing liver toxicity. A number of studies have shown the safety of statins in patients with liver disease[31-33]. Our study particularly evaluated these issues in cirrhotic patients and our safety evaluation included Bil, ALP, GGT, ALT, AST, CPK and questionnaire for muscle weakness at 15th and 30th day of treatment. There was no major safety concern seen in our study. Some minor adverse events which were observed after addition of simvastatin are: (1) muscle weakness with CPK > 5 times in one patient and was withdrawn; (2) prurutis in one patient which settled and treatment continued; (3) diarrhea in one patient, self-settled and treatment continued; (4) severe dizziness and treatment withdrawn; and (5) hepatic encephalopathy in one patient and withdrawn from the study, not related to simvastatin likely part of disease.

However, whether safety profile is maintained after long term administration needs further long term studies especially with larger doses in advanced liver disease. Newer drugs like rovastatin have been shown to be safe in chronic liver disease also.

Overall, 7 patients had adverse events, 4 (57.1%) among responders, and 3 (42.9%) among non-responders with no statistical significance. Three patients were withdrawn due to side effects, first one because of increase in CPK > 5 times with muscle weakness, second one developed dizziness and 3rd patients developed hepatic encephalopathy not related to simvastatin. Liver function test after 30 d and CPK did not change and remained static and no further side effects were observed after 30 d.

Thus in conclusion, our study is first study which clearly shows that a sequential treatment strategy is an excellent policy in the pharmacological management of portal hypertension by which around 80% of response can be achieved. Further long term safety profile of statins with large doses particularly in advanced disease needs further studies and safe drugs like provastatin needs to be evaluated in future that can be used for adjuvant treatment along with carvedilol.

COMMENTS

Background

Carvedilol, a potent 3rd generation non-selective beta blocker (NSBB) has shown to be a promising therapy for reduction of portal hypertension. Although up to 60% of patients respond to carvedilol, options for carvedilol non responders in patients with portal hypertension is limited. Simvastatin improves liver generation of NO and hepatic endothelial dysfunction in patients with cirrhosis without affecting the hemodynamics such as heart rate and blood pressure. Hence, it could be used as an effective adjuvant therapy with carvedilol without causing any major side effects in patients with portal hypertension.

Research frontiers

Current guidelines recommend using NSBB, such as propranolol or nadolol, with or without isosorbide-5-mononitrate to prevent variceal bleeding. Carvedilol, which blocks both α and β receptors, was shown to have better results than NSBBs by further reducing intrahepatic resistance and thus, could be used for propranolol non-responders. However, treatment option for carvedilol non-responders has not been studied yet.

Innovations and breakthroughs

Addition of simvastatin could be an important pharmacological rescue therapy for carvedilol nonresponders. This study showed that addition of simvastatin to carvedilol non responders can increase overall response to around 80%, which is one of the best possible pharmacologically produced chronic response and may open a new strategy for the treatment of portal hypertension.

Applications

Addition of simvastatin to carvedilol non-responders may prove to be an excellent therapy in patients with portal hypertension.

Terminology

NSBB are very useful drugs in preventing first variceal bleeding and re-bleeding in patients with cirrhosis.

Peer-review

The observational study of Wani *et al* seems to be the first which demonstrate that a sequential treatment (carvedilol + simvastatin) strategy is an excellent policy in the pharmacological management of portal hypertension. The study is well designed and well presented.

REFERENCES

1 **Groszmann RJ**, Garcia-Tsao G, Bosch J, Grace ND, Burroughs AK, Planas R, Escorsell A, Garcia-Pagan JC, Patch D, Matloff DS, Gao H, Makuch R. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. *N Engl J Med* 2005; **353**: 2254-2261 [PMID: 16306522 DOI: 10.1056/NEJMoa044456]

2 **Ripoll C**, Groszmann R, Garcia-Tsao G, Grace N, Burroughs A, Planas R, Escorsell A, Garcia-Pagan JC, Makuch R, Patch D, Matloff DS, Bosch J. Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. *Gastroenterology* 2007; **133**: 481-488 [PMID: 17681169 DOI: 10.1053/j.gastro.2007.05.024]

3 **Ripoll C**, Groszmann RJ, Garcia-Tsao G, Bosch J, Grace N, Burroughs A, Planas R, Escorsell A, Garcia-Pagan JC, Makuch R, Patch D, Matloff DS. Hepatic venous pressure gradient predicts development of hepatocellular carcinoma independently of severity of cirrhosis. *J Hepatol* 2009; **50**: 923-928 [PMID: 19303163 DOI: 10.1016/j.jhep.2009.01.014]

4 **Abraldes JG**, Tarantino I, Turnes J, Garcia-Pagan JC, Rodés J, Bosch J. Hemodynamic response to pharmacological treatment of portal hypertension and long-term prognosis of cirrhosis. *Hepatology* 2003; **37**: 902-908 [PMID: 12668985 DOI: 10.1053/jhep.2003.50133]

5 **Albillos A**, Bañares R, González M, Ripoll C, Gonzalez R, Catalina MV, Molinero LM. Value of the hepatic venous pressure gradient to monitor drug therapy for portal hypertension: a meta-analysis. *Am J Gastroenterol* 2007; **102**: 1116-1126 [PMID: 17391317 DOI: 10.1111/j.1572-0241.2007.01191.x]

6 **Pugh RN**, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973; **60**: 646-649 [PMID: 4541913]

7 **Gluud LL**, Klingenberg S, Nikolova D, Gluud C. Banding ligation versus beta-blockers as primary prophylaxis in esophageal varices: systematic review of randomized trials. *Am J Gastroenterol* 2007; **102**: 2842-2848; quiz 2841, 2849 [PMID: 18042114 DOI: 10.1111/j.1572-0241.2007.01564.x]

8 **Tripathi D**, Graham C, Hayes PC. Variceal band ligation versus beta-blockers for primary prevention of variceal bleeding: a meta-analysis. *Eur J Gastroenterol Hepatol* 2007; **19**: 835-845 [PMID: 17873606 DOI: 10.1097/MEG.0b013e3282748f07]

9 **Garcia-Tsao G**, Bosch J. Management of varices and variceal hemorrhage in cirrhosis. *N Engl J Med* 2010; **362**: 823-832 [PMID: 20200386 DOI: 10.1056/NEJMra0901512]

10 **Bureau C**, Péron JM, Alric L, Morales J, Sanchez J, Barange K, Payen JL, Vinel JP. "A La Carte" treatment of portal hypertension: Adapting medical therapy to hemodynamic response for the prevention of bleeding. *Hepatology* 2002; **36**: 1361-1366 [PMID: 12447860 DOI: 10.1053/jhep.2002.36945]

11 **Abraldes JG**, Albillos A, Bañares R, Turnes J, González R, García-Pagán JC, Bosch J. Simvastatin lowers portal pressure in patients with cirrhosis and portal hypertension: a randomized controlled trial. *Gastroenterology* 2009; **136**: 1651-1658 [PMID: 19208350 DOI: 10.1053/j.gastro.2009.01.043]

12 **Wani ZA**, Bhat RA, Bhadori AS, Zargar SA, Shah AH, Maiwall R, Hameedand I, Syed B. A Haemodynamic Analysis to Assess the Safe Dose of Carvedilol across Different Child Class of Liver Disease. *BJMMR* 2015; **7**: 355-368 [DOI: 10.9734/BJMMR/2015/15398]

13 **Wani ZA**, Baht RA, Bhadoria AS, Maiwall R, Majeed Y, Khan AA, Zargar SA, Shah MA, Khan KM. After proper optimization of carvedilol dose, do different child classes of liver disease differ in terms of dose tolerance and response on a chronic basis? *Saudi J Gastroenterol* 2015; **21**: 278-283 [PMID: 26458853 DOI: 10.4103/

1319-3767.164207]
14 **Bosch J**, Abraldes JG, Groszmann R. Current management of portal hypertension. *J Hepatol* 2003; **38** Suppl 1: S54-S68 [PMID: 12591186]
15 **Failli P**, DeFRANCO RM, Caligiuri A, Gentilini A, Romanelli RG, Marra F, Batignani G, Guerra CT, Laffi G, Gentilini P, Pinzani M. Nitrovasodilators inhibit platelet-derived growth factor-induced proliferation and migration of activated human hepatic stellate cells. *Gastroenterology* 2000; **119**: 479-492 [PMID: 10930383]
16 **Yu Q**, Shao R, Qian HS, George SE, Rockey DC. Gene transfer of the neuronal NO synthase isoform to cirrhotic rat liver ameliorates portal hypertension. *J Clin Invest* 2000; **105**: 741-748 [PMID: 10727442 DOI: 10.1172/JCI7997]
17 **Van de CM**, Omasta A, Janssens S. In vivo gene transfer of endothelial nitric oxide synthase decreases portal pressure in anaesthetized carbon tetrachloride cirrhotic rats. *Gut* 2002; **51**: 440-445
18 **Morales-Ruiz M**, Cejudo-Martín P, Fernández-Varo G, Tugues S, Ros J, Angeli P, Rivera F, Arroyo V, Rodés J, Sessa WC, Jiménez W. Transduction of the liver with activated Akt normalizes portal pressure in cirrhotic rats. *Gastroenterology* 2003; **125**: 522-531 [PMID: 12891555]
19 **Wiest R**, Groszmann RJ. The paradox of nitric oxide in cirrhosis and portal hypertension: too much, not enough. *Hepatology* 2002; **35**: 478-491 [PMID: 11826425 DOI: 10.1053/jhep.2002.31432]
20 **Kiszka-Kanowitz M**, Henriksen JH, Møller S, Bendtsen F. Blood volume distribution in patients with cirrhosis: aspects of the dual-head gamma-camera technique. *J Hepatol* 2001; **35**: 605-612 [PMID: 11690706]
21 **Huonker M**, Schumacher YO, Ochs A, Sorichter S, Keul J, Rössle M. Cardiac function and haemodynamics in alcoholic cirrhosis and effects of the transjugular intrahepatic portosystemic stent shunt. *Gut* 1999; **44**: 743-748 [PMID: 10205217]
22 **Bosch J**, Garcia-Pagán JC, Berzigotti A, Abraldes JG. Measurement of portal pressure and its role in the management of chronic liver disease. *Semin Liver Dis* 2006; **26**: 348-362 [PMID: 17051449 DOI: 10.1055/s-2006-951603]
23 **Tarantino G**, Citro V, Conca P, Riccio A, Tarantino M, Capone D, Cirillo M, Lobello R, Iaccarino V. What are the implications of the spontaneous spleno-renal shunts in liver cirrhosis? *BMC Gastroenterol* 2009; **9**: 89 [PMID: 19930687 DOI: 10.1186/1471-230X-9-89]
24 **Tarantino G**, Citro V, Esposito P, Giaquinto S, de Leone A, Milan G, Tripodi FS, Cirillo M, Lobello R. Blood ammonia levels in liver cirrhosis: a clue for the presence of portosystemic collateral veins. *BMC Gastroenterol* 2009; **9**: 21 [PMID: 19292923 DOI: 10.1186/1471-230X-9-21]
25 **Bañares R**, Moitinho E, Matilla A, García-Pagán JC, Lampreave JL, Piera C, Abraldes JG, De Diego A, Albillos A, Bosch J. Randomized comparison of long-term carvedilol and propranolol administration in the treatment of portal hypertension in cirrhosis. *Hepatology* 2002; **36**: 1367-1373 [PMID: 12447861 DOI: 10.1053/jhep.2002.36947]
26 **Tripathi D**, Therapondos G, Lui HF, Stanley AJ, Hayes PC. Haemodynamic effects of acute and chronic administration of low-dose carvedilol, a vasodilating beta-blocker, in patients with cirrhosis and portal hypertension. *Aliment Pharmacol Ther* 2002; **16**: 373-380 [PMID: 11876689]
27 **Stanley AJ**, Therapondos G, Helmy A, Hayes PC. Acute and chronic haemodynamic and renal effects of carvedilol in patients with cirrhosis. *J Hepatol* 1999; **30**: 479-484 [PMID: 10190732]
28 **Silkauskaitė V**, Kupčinskas J, Pranculis A, Jonaitis L, Petrenkienė V, Kupčinskas L. Acute and 14-day hepatic venous pressure gradient response to carvedilol and nebivolol in patients with liver cirrhosis. *Medicina* (Kaunas) 2013; **49**: 467-473 [PMID: 24823927 DOI: 10.1016/S0168-8278(09)60228-2]
29 **Abraldes JG**, Rodríguez-Vilarrupla A, Graupera M, Zafra C, García-Calderó H, García-Pagán JC, Bosch J. Simvastatin treatment improves liver sinusoidal endothelial dysfunction in CCl4 cirrhotic rats. *J Hepatol* 2007; **46**: 1040-1046 [PMID: 17335931 DOI: 10.1016/j.jhep.2007.01.020]
30 **Trebicka J**, Hennenberg M, Laleman W, Shelest N, Biecker E, Schepke M, Nevens F, Sauerbruch T, Heller J. Atorvastatin lowers portal pressure in cirrhotic rats by inhibition of RhoA/Rho-kinase and activation of endothelial nitric oxide synthase. *Hepatology* 2007; **46**: 242-253 [PMID: 17596891 DOI: 10.1002/hep.21673]
31 **Ritzel U**, Leonhardt U, Näther M, Schäfer G, Armstrong VW, Ramadori G. Simvastatin in primary biliary cirrhosis: effects on serum lipids and distinct disease markers. *J Hepatol* 2002; **36**: 454-458 [PMID: 11943414]
32 **Chalasani N**. Statins and hepatotoxicity: focus on patients with fatty liver. *Hepatology* 2005; **41**: 690-695 [PMID: 15789367 DOI: 10.1002/hep.20671]
33 **Vuppalanchi R**, Teal E, Chalasani N. Patients with elevated baseline liver enzymes do not have higher frequency of hepatotoxicity from lovastatin than those with normal baseline liver enzymes. *Am J Med Sci* 2005; **329**: 62-65 [PMID: 15711421]

P- Reviewer: Sargsyants N, Sipos F, Tarantino G **S- Editor**: Ji FF
L- Editor: A **E- Editor**: Li D

World Journal of Hepatology

Submit a Manuscript: http://www.wjgnet.com/esps/

World J Hepatol 2017 February 18; 9(5): 278-287

DOI: 10.4254/wjh.v9.i5.278

ISSN 1948-5182 (online)

SYSTEMATIC REVIEWS

Influence of vitamin D on liver fibrosis in chronic hepatitis C: A systematic review and meta-analysis of the pooled clinical trials data

Alia S Dadabhai, Behnam Saberi, Katie Lobner, Russell T Shinohara, Gerard E Mullin

Alia S Dadabhai, Behnam Saberi, Katie Lobner, Gerard E Mullin, Division of Gastroenterology and Hepatology, the Johns Hopkins University School of Medicine, Baltimore, MD 21224, United States

Russell T Shinohara, Department of Biostatistics and Epidemiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104, United States

Author contributions: Dadabhai AS, Saberi B and Mullin GE contributed equally to the data evaluation, manuscript preparation, editing, figures, and final submission; Shinohara RT provided biostatistics methodology oversight, data extractions and meta-analysis with pooled data figure preparation and manuscript preparation and editing; Lobner K provided informatics methodology support, conducted the literature search, and reviewed and edited the manuscript.

Conflict-of-interest statement: All the authors declare that they have no competing interests.

Data sharing statement: Technical appendix, statistical code, and dataset are available from the corresponding author at adadabh1@jhmi.edu.

Manuscript source: Invited manuscript

Correspondence to: Alia S Dadabhai, MD, Assistant Professor, Division of Gastroenterology and Hepatology, the Johns Hopkins University School of Medicine, 4940 Eastern Ave A504, Baltimore, MD 21224, United States. adadabh1@jhmi.edu
Telephone: +1-410-5507857
Fax: +1-410-5507861

Received: November 16, 2016
Peer-review started: November 21, 2016
First decision: December 1, 2016
Revised: December 14, 2016
Accepted: January 2, 2017
Article in press: January 3, 2017
Published online: February 18, 2017

Abstract

AIM

To investigate the relationship between vitamin D and liver fibrosis in hepatitis C-monoinfected or hepatitis C virus (HCV)-human immunodeficiency virus (HIV) co-infected patients.

METHODS

Pertinent studies were located by a library literature search in PubMed/Embase/Cochrane/Scopus/LILACS by two individual reviewers. Inclusion criteria: (1) studies with patients with HCV or co-infected HCV/HIV; (2) studies with patients ≥ 18 years old; (3) studies that evaluated liver fibrosis stage, only based on liver biopsy; and (4) studies that reported serum or plasma 25(OH)D levels. Studies that included pediatric patients, other etiologies of liver disease, or did not use liver biopsy for fibrosis evaluation, or studies with inadequate data were excluded. Estimated measures of association reported in the literature, as well as corresponding measures of uncertainty, were recorded and corresponding odds ratios with 95%CI were included in a meta-analysis.

RESULTS

The pooled data of this systematic review showed that 9 of the 12 studies correlated advanced liver disease defined as a Metavir value of F3/4 with 25(OH) D level insufficiency. The meta-analysis indicated a significant association across studies.

CONCLUSION
Low vitamin D status is common in chronic Hepatitis C patients and is associated with advanced liver fibrosis.

Key words: Vitamin D; Liver fibrosis; Hepatitis C virus; Chronic hepatitis C

Core tip: Vitamin D levels are associated with more advanced fibrosis in chronic hepatitis C.

Dadabhai AS, Saberi B, Lobner K, Shinohara RT, Mullin GE. Influence of vitamin D on liver fibrosis in chronic hepatitis C: A systematic review and meta-analysis of the pooled clinical trials data. *World J Hepatol* 2017; 9(5): 278-287 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i5/278.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i5.278

INTRODUCTION

Hepatitis C virus (HCV) infection remains one of the most common etiologies of liver disease worldwide. A number of epidemiological papers have addressed the global prevalence of Hepatitis C. Lanini *et al*[1] reported that 100 million people globally have serological evidence of current or past HCV infection causing 700000 deaths annually while others suggest that the actual occurrence is double[2]. HCV remains the most common indication for liver transplantation in the United States[3]. Chronic infection with HCV can lead to liver inflammation, liver fibrosis, cirrhosis, and hepatocellular carcinoma. Liver fibrosis is a result of excessive accumulation of extracellular matrix proteins, as part of the wound healing response to chronic injury and chronic inflammation[4]. Various factors have been associated with progression of fibrosis including duration of infection, age, male sex, diabetes, alcohol consumption and human immunodeficiency virus (HIV) co-infection[5].

Vitamin D is a hormone that has numerous biological properties that influence host physiology by regulating epigenetic regulation of more than 2000 genes throughout the body. Vitamin D is best known for its role in maintaining bone mineralization but has diverse and profound influences which can determine disease development and outcome. Although referred to as a vitamin, this steroid hormone is synthesized in the body by a series of hydroxylation reactions that occur in skin (7-hydroxylation), the liver (25-hydroxylation) and the kidney (1-hydroxylation)[6] (Figure 1). Reduction of the enzymatic conversion of 7-dehydrocholesterol to 1.25 hydroxy vitamin D at any of the three conversion steps can result in suboptimal vitamin D status[7]. Vitamin D has a number of influences on innate and adaptive immunity which are pertinent to study in conditions that are driven by chronic inflammation and maladaptive tissue injury[8,9]. Given the ubiquitous distribution of vitamin D receptors in virtually every cell in the body-suboptimal vitamin D status has been studied for its relationship to numerous diseases[10]. For example, there is substantial evidence that vitamin D benefits rheumatoid arthritis, due to its immunomodulatory effect[11]. The role of vitamin D in various cancers has been established linked to its anti-proliferative action mediated through vitamin D nuclear receptor[12]. There have been numerous reports on lower serum vitamin D levels in patients with chronic liver disease from various etiologies[13]. In chronic HCV, Low vitamin D levels have been reported in 46% to 92% of patients[10] raising suspicion of its potential contribution to disease pathogenesis. There is growing evidence from various groups, that vitamin D levels are inversely correlated with liver inflammation and stage of liver fibrosis in patients with HCV; however, the studies are heterogeneous with occasionally the results are conflicting. Additionally, the methods of reporting liver fibrosis were variable.

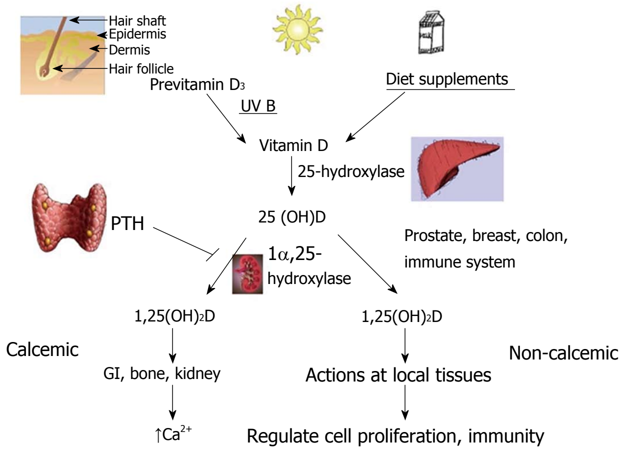

Figure 1 Vitamin D metabolism. Vitamin D has diverse influences throughout the body as vitamin D receptors present on virtually every cell. The actions of vitamin D can be subdivided into two larger categories: Calcemic and non-calcemic actions. The non-calcemic actions of vitamin D are legion and have been reviewed elsewhere[6,54-58]. Reproduced with permission[6].

The aim of this study was to evaluate the relationship between vitamin D status and hepatic fibrosis based on histopathological staging in patients with chronic HCV mono-infection or co-infected HIV-HCV infection, by performing a systematic review of the scientific literature followed by a meta-analysis.

MATERIALS AND METHODS

Search method

Applicable studies were identified by a library literature search in Pubmed/Embase/Cochrane/Scopus/LILACS utilizing the PRISMA checklist[14] "Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated" and the Cochrane review reporting guidelines (6.6.2.2)[15].

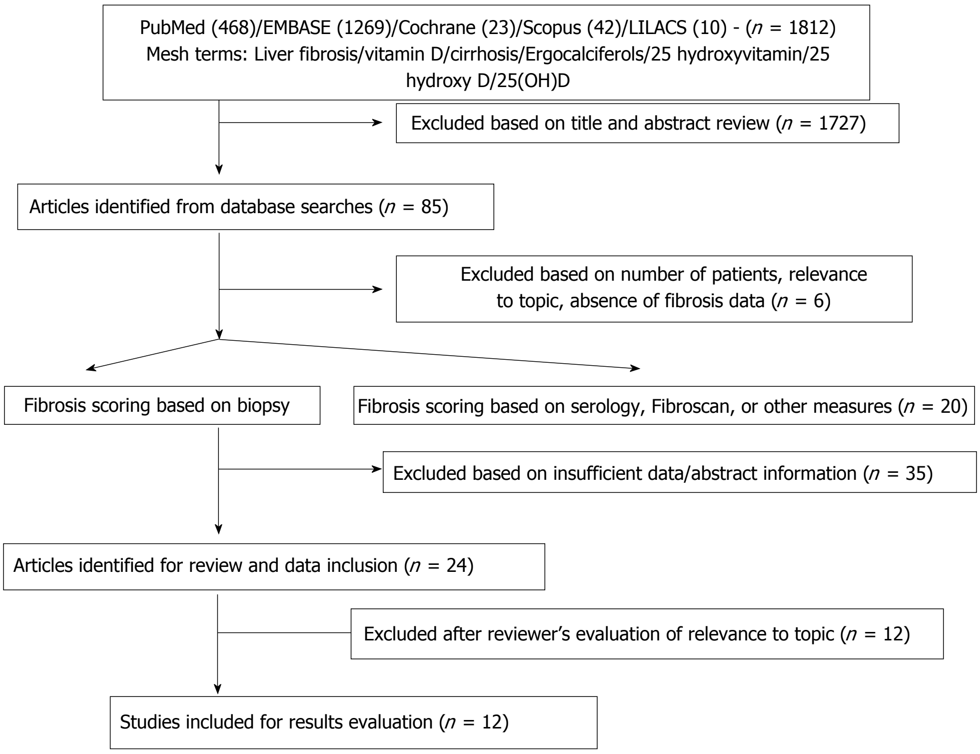

Figure 2 Flowchart of study selection process. Eighteen hundred and twelve articles were identified using PubMed (n = 468)/EMBASE (n = 1269)/Cochrane (n = 23)/Scopus (n = 42)/LILACS (n = 10) search engines. Detailed evaluation of the articles by at least two independent reviewers (total of three) narrowed the studies to twelve (n = 2521) based upon inclusion and exclusion criteria as listed in Table 1.

The search terms were as follows: ["Liver cirrhosis" or "liver" and ("cirrhosis" or "fibrosis")] and ["vitamin D" or "Ergocalciferols" or "25 hydroxyvitamin D" or "25 hydroxy vitamin D" or "25 hydroxy D" or "25(OH)D"]. Also, the studies cited by the selected articles were searched for further pertinent studies. The search was performed before July 6, 2016.

Selection criteria

The title and abstract of the studies were carefully reviewed by two individual reviewers, based on the inclusion and exclusion criteria. If there was an agreement between two reviewers, then the study was selected for further analysis. When there was a disagreement, a third reviewer determined if the study qualified for inclusion. Once the articles met the criteria, then the text was reviewed, and data extraction was completed.

Inclusion criteria: (1) studies with patients with HCV or co-infected HCV/HIV; (2) studies with patients ≥ 18 years old; (3) studies that evaluated liver fibrosis stage, only based on liver biopsy; and (4) studies that reported serum or plasma 25(OH)D levels. Exclusion criteria: (1) liver diseases other than hepatitis C; (2) studies with inadequate data; (3) studies that used non-invasive methods in evaluating liver fibrosis; and (4) age < 18 years.

Data extraction

A total of 12 studies were included for extraction which was performed by two independent reviewers based on data quality, sufficiency, and relevance. Disagreements were resolved by a third reviewer to reach a consensus. The following data were extracted: Last name of the first author, demographic information of patients, publication year, sample size, HCV genotype, presence or absence of HIV co-infection, pathological fibrosis stage using Metavir score, vitamin D levels, and association of serum vitamin D level and fibrosis stage (Figure 2). The quality of evidence was ascertained by two independent reviewers using The Grading of Recommendations Assessment, Development and Evaluation (GRADE) analysis whereby very low = 1, low = 2, moderate = 3, high = 4[16]. The strength of recommendations were 1 (strong) or 2 (weak)[17]. When there was a disagreement, a third reviewer determined GRADE assessment and strength of recommendations.

Statistical analysis

All statistical computations were conducted in R (Version 3.3.1, R Foundation for Statistical Computing, Vienna, Austria, 2016)[18]. Estimated odds ratios (OR) reported in the literature, as well as 95%CI, were inverted when necessary and included in a meta-analysis. In several studies, the odds ratio for severe fibrosis corresponding to vitamin D deficiency was not reported, but the distribution (mean and standard deviation or inter-quartile range) of vitamin D levels were reported for subjects with and without severe fibrosis separately. To estimate the odds ratio from these studies, a Monte Carlo simulation approach was adopted: For each such study, 1000

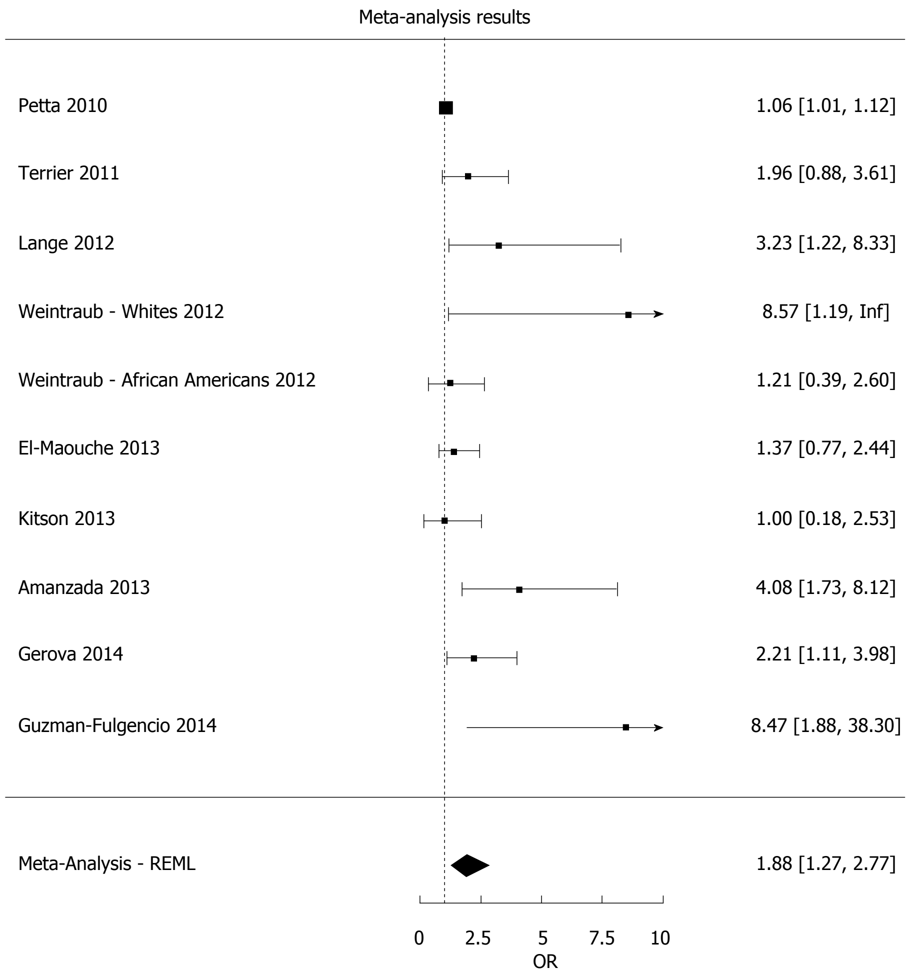

Figure 3 Meta-analysis of the pooled data from the 12 included studies. The odds ratio for severe fibrosis comparing low vitamin D levels was estimated by meta-analyzing studies including a total of 2521 patients. Details concerning the analytic strategy are provided in the Materials and Methods section.

simulated studies were created assuming that vitamin D levels were normally distributed with the reported parameters and the observed number of subjects in each group. The odds ratio for severe fibrosis comparing vitamin D levels with a cutoff of 15 ng/mL was estimated for each simulated dataset. A sensitivity analysis was also conducted by using thresholds of 20 ng/mL and 30 ng/mL. The average odds ratio across simulated datasets were then estimated, and quantile-based confidence intervals were also recorded and included into the meta-analysis. A random-effects meta-analysis fit using restricted maximum likelihood was then fit using the Metafor package in R[19]. $P < 0.05$ was considered statistically significant.

RESULTS

The initial protocol established a series of mesh terms used to identify articles that would evaluate the severity of liver fibrosis in chronic hepatitis C patients with vitamin D levels. Eighteen hundred and twelve articles were found using PubMed (n = 468)/EMBASE (n = 1269)/Cochrane (n = 23)/Scopus (n = 42)/LILACS (n = 10) search engines. Mesh terms used were liver fibrosis/vitamin d/cirrhosis/Ergocalciferols/25 hydroxyvitamin/25 hydroxy d/25(OH) D. Detailed evaluation of the articles by at least two independent reviewers (total of three) assessed the sufficiency of data, method of fibrosis qualification, relevance to the topic to narrow the studies to twelve. The data extraction algorithm is summarized in Figure 3. Table 1 reflects the characteristics of the studies relating fibrosis to chronic hepatitis C and vitamin D level. When patients were stratified according to vitamin D status, we found substantial differences between the levels of severity of liver fibrosis. The sensitivity analysis with different cutoffs for the Monte Carlo simulations showed robustness of the result to the choice of cutoff, with significant effects for all thresholds employed.

Definition of vitamin D levels

Vitamin D insufficiency was defined in most studies as below < 30 ng/mL, and deficiency ranged from < 20 ng/mL to 10 ng/mL. While there was some variability in these definitions, there was consistency in the lower limit of normal being < 30 ng/mL. Two of the studies used nmol/L to express 25(OH)D, but were consistent with vitamin D insufficiency below the lower limit of normal < 80 nmol/L.

Table 1 Pooled data of vitamin D levels and liver fibrosis from the 12 included studies

Year	Author	Country	Design	*n*	HCV GT	HIV	Definition of vitamin D insufficiency (I)/deficiency (D)	Outcome (serum vitamin D and liver fibrosis)	*P* value/OR 95%CI	GRADE quality of evidence very low = 1, low = 2, moderate = 3, high = 4 and strength of recommendation: 2 = strong 1 = weak
2010	Petta	Italy	Prospective	197	1	No	< 30 ng/mL for low vitamin D level	Low 25(OH)D associated with severe fibrosis (F3/F4)	0.942 [0.893, 0.994] *P* = 0.009	GRADE 3 Strong
2011	Terrier	France	Prospective	189	1,-4 other	Yes	< 10 ng/mL D, 10-30 ng/mL (I)	Low 25(OH)D correlate with severe fibrosis (F3/F4)	*P* = 0.04	GRADE 3 Strong
2012	Lange	Sweden	Retrospective	496	1, 4	No	< 10 ng/mL D, < 20 ng/mL (I)	Advanced fibrosis stage F2-F4 *vs* F0-F1 associated with low 25(OH)D	0.31 [0.12, 0.82] *P* = 0.018	GRADE 2 Weak
2012	Weintraub	United States	Cross-sectional	171	1	No	< 20 ng/mL or < 30 ng/mL (I)	Higher 25(OH)D predictive of milder fibrosis (F0-F2) in white patients but not in African Americans	*P* = 0.007	GRADE 2 Weak
2012	Baur	Switzerland	Cohort	251	1, 3	No	< 20 ng/mL (I)	(1) 25(OH)D lower in more advanced fibrosis (F2 *vs* F0-1); (2) low 25-OH vitamin D associated with rapid fibrosis progression rate.	*P* = 0.005, *P* = 0.013	GRADE 3 Strong
2013	El-Maouche	United States	Prospective	116	-	Yes	< 15 ng/mL (D)	(1) The prevalence of significant fibrosis (F2 ⩾ 2) was similar among those with and without low Vitamin D; (2) low 25(OH)D not associated with significant fibrosis after adjusting for other confounders	*P* = 0.43 1.37 [0.77, 2.44]	GRADE 3
2013	Mandorfer	Austria	Prospective	65	1, 4	Yes	< 10 ng/mL D, 10-30 ng/mL (I)	Patients with D-DEF displayed a higher prevalence of advanced liver	*P* = 0.009	Strong GRADE 3
2013	Kitson	Australia and New Zealand	Prospective	274	1	No	< 50 nmol/L D < 75 nmol/L (I)	Fibrosis than patients with D-NORM Baseline 25(OH)D level did not vary with fibrosis stage (F3/4 *vs* F0-2)	*P* = 0.18	Strong GRADE 3
2013	Amanzada	Germany	Prospective	191	1	Yes	< 30 ng/mL (I)	Low 25(OH)D associated with advance fibrosis (F0-2 *vs* F3/4)	*P* = 0.02	Strong GRADE 3
2014	Gerova	Bulgaria	Retrospective	296	1, 4	No	< 25 nmol/L (D), 25-50 nmol/L for profound (I), 50 –80 nmol/L for mild (I)	Lower 25OHD levels were registered in cases with advanced fibrosis compared to those with mild or absent fibrosis	*P* >0.05	Strong GRADE 2
2014	Guzman-Fulgencio	Spain	Retrospective	174	1, 4	Yes	< 10 ng/mL (D), 10-30 ng/mL (I)	Low 25(OH)D deficiency associated with advanced fibrosis (F3/4 *vs* F0-2)	*P* = 0.005	Weak GRADE 2
2015	Esmat	Egypt	Prospective	101	4	No	< 20 ng/mL (D), 20-30 (I)	No correlation found between vitamin D levels and stage of liver fibrosis	*P* = 0.26	Weak GRADE 3

HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; GRADE: Grading of Recommendations Assessment, Development and Evaluation.

Table 2 Selection criteria for inclusion and exclusion

Inclusion criteria
Age ≥ 18 yr
Studies including mono-infected HCV or co-infected HCV/HIV
Studies that evaluated liver fibrosis stage, only based on liver histology
Studies that reported serum or plasma 25(OH)D levels
Exclusion criteria
Age < 18 yr
Other etiologies of liver disease, other than hepatitis C
Studies that used non-invasive methods in evaluating liver fibrosis
Inadequate data

HCV: Hepatitis C virus; HIV: Human immunodeficiency virus.

Association between vitamin D deficiency and severity of liver disease

Among the articles used for data extraction, there were seven prospective studies, three retrospective studies, one cross-sectional analysis, and one cohort study (Table 1). In a review of the results, nine studies demonstrated a significant association between plasma levels of vitamin D and degree of HCV-related hepatic fibrosis. Three studies showed no correlation was found between vitamin D levels and stage of liver fibrosis. Patient characteristics between these studies were all similar and could not account for the variability of the findings between the three negative studies and the nine positive studies. Only one of the three negative studies was conducted in the northern hemisphere. Overall, hepatitis C genotypes were not different among the negative studies, although El-Maouche *et al*[20] did not identify which genotype(s) were included. The forest plot of the data used in this systematic review showed that advanced liver disease defined as a Metavir value of F3/4 was associated with severe 25(OH)D insufficiency as follows; OR (95%CI): 1.88 (1.27, 2.77), and I^2 (total heterogeneity/total variability): 66.94% indicated substatial heterogeneity between studies.

Plasma vitamin D levels and seasonal variation

Notably there were several latitudes identified in the studies which can affect Vitamin D levels, however, the scope of this difference in this analysis's outcome was not assessed. In the article by Guzmán-Fulgencio *et al*[21] significant seasonal variation of plasma 25(OH)D levels was observed with the subjects in the first semester (winter/spring) having lower plasma 25(OH)D levels than patients evaluated in the second semester (summer/autumn) (P < 0.001). A higher percentage of patients with vitamin D deficiency (25(OH)D < 25 nmol/L) was found in the first semester (winter/spring) (P < 0.001). Since not all the studies identified the time frame of vitamin D levels and biopsy procurement, we were unable to qualify the significance of this on the study results.

DISCUSSION

The results of our systematic analysis of the literature demonstrated an association between advanced liver fibrosis (defined as Metavir F3/F4) in chronic hepatitis C (CHC) with vitamin D status as reflected by 25-hydroxyvitamin D [25(OH)D] serum levels. In nine[21-29] of twelve studies (75%) that qualified for data extraction (Tables 1 and 2) the final analysis demonstrated an overall association between low vitamin D status as defined as serum 25(OH)D < 15 ng/mL with advanced liver fibrosis (F3/F4 stage disease) in CHC as proven by biopsy analysis for fibrosis stage. These data are highly consistent with prior reports, and the expected pathophysiological interference of 25-hydroxylation of vitamin D as liver fibrosis increases and functional hepatic capacity decreases over the course of hepatitis C disease progression[6].

A recent systematic review of the literature by Abbasi *et al*[30] studied the relationship between low vitamin D status [< 20 ng/mL 25 OH(D)] and the severity of the CLD. A comparatively abridged search strategy yielded 641 articles for consideration and ultimately 19 articles and 4895 study patients with CLD for data extraction showing that almost 80% of patients with chronic liver disease had severe vitamin D deficiency. García-Álvarez *et al*[31] conducted a systematic review evaluating the relationship of vitamin D status to advanced liver fibrosis in CHC-naïve patients and sustained virological response (SVR) to therapy using pegylated interferon/ribavirin (Peg-IFN/RBV). Seven of fourteen papers utilized for their extraction evaluated advanced liver fibrosis (1083 patients) and eleven for SVR (2672 patients). Approximately 70% of CHC patients had low 25(OH)D whereby the definition of insufficiency varied (20 or 30 ng/mL), and 50% of the HCV-infected patients had 25(OH)D levels < 10 or 20 ng/mL. Overall, low vitamin D status was related to a diagnosis of advanced stage of liver disease. Luo et al utilized a search methodology restricted to PubMed and Embase databases before October 2013 included studies that analyzed the association between serum vitamin D status and the severity of liver fibrosis in 8231 CHC patients without other restrictions yielding six global studies for data extraction[13]. One study recruited 6567 participants as part of the Swiss Hepatitis C Cohort Study[23] raising concerns for skewing of the extracted data. The mean data from extracted studies suggested that lower serum vitamin D is a risk factor for progressive liver fibrosis in CHC patients. However, there was a high heterogeneity and inconsistencies depending upon data set utilized (OR data studies *vs* mean data extracted). Our search methodology instead included 2521 patients which incorporated the 2012 study by Lange *et al*[32] which evaluated 468 HCV patients treated with alpha interferon-based regimens for vitamin D status and advanced disease demonstrating that fibrosis stages F2-F4 *vs* F0-F1 associated with low 25(OH)D.

The nine studies showing a positive association between low vitamin D with an advanced stage of fibrosis had variations in their definition of vitamin D status which challenged our ability to Meta-analyze the data. Low vitamin D was stratified according to by either insufficient (I) or deficient (D) (Table 1) in eight[21-27,29] of the nine studies. Gerova *et al*[28] used three categories; mild insufficiency, profound insufficiency, and deficiency. Overall, of the twelve papers in our final analysis, two[28,33] utilized nmol/L to measure serum 25(OH) vitamin D status. Insufficiency was defined as < 30 ng/mL in seven with another two using equivalent levels in nmol/L[28,34], < 20 ng/mL in two[23,25] while El-Maouche studied only deficient patients (< 15 ng/mL)[20]. The definition of "deficiency" was utilized by all but two[20,34] of the studies as < 10 ng/mL 25(OH) vitamin D. The prevalence of vitamin D deficiency in a population depends on upon the definition used [< 20 or < 30 ng/mL (50 or 75 nmol/L)]. In the National Health and Nutrition Examination Survey (NHANES), 41.6 percent of United States adults had (25[OH]D) levels < 20 ng/mL (50 nmol/L)[35]. The Institute of Medicine recommends the attainment of the serum 25(OH)D levels of > 20 < 40 ng/mL (50 to 100 nmol/L), however, many define sufficient vitamin D status as 25(OH)D > 30 and < 50 ng/mL (75 to 125 nmol/L)[36,37].

Hepatitis C genotype (1-6) did not change the outcome of analyses between advanced fibrosis in CHC with vitamin D status[20,33,34]. The geographical latitudes of study site and variable seasonal fluctuations have provided challenges to vitamin D status, but did not appear to influence the outcome of the negative outcome studies[20,33,34] Esmat *et al*[34] conducted a open-labelled RCT of 101 HVC4 Egyptian patients undergoing standard of care (SOC) Peg-IFN/RBV plus/minus 15000 IU vitamin D_3 (cholecalciferol). The fibrosis stage (F1-F3) at baseline was not different according to 25(OH) vitamin D levels. El-Maouche *et al*[20] evaluated HIV-HCV co-infected patients for histological fibrosis using the Metavir system [0 (no fibrosis) to 4 (cirrhosis)] and used banked serum as a source for vitamin D determination. Similar to Esmat *et al*[34], the prevalence of significant fibrosis (F2 ≥ 2) was similar among those with and without low vitamin D while low 25(OH)D status was not associated with significant fibrosis after adjusting for other confounders. Finally, Kitson *et al*[38] from Australia evaluated pre-treatment 25-hydroxyvitamin D [25(OH)D] level in a cohort of 274 treatment-naive patients with HCV-1 to evaluate the association between vitamin D status, virological response, and liver histology after 48 wk of pegylated interferon alfa-2a plus ribavirin therapy. Baseline 25(OH)D level did not vary with fibrosis stage (F3/4 *vs* F0-2).

The manner by which vitamin D may influence the course of CHC may be due to effects on viral clearance, immune modulation, cell differentiation and proliferation and inflammation regulation. Vitamin D is not only involved in calcium homeostasis but has also has been associated with the mechanism of cellular proliferation, and immunomodulation[39]. Several studies have shown that vitamin D levels are inversely correlated with stage of liver fibrosis in patients with CHC. Nine[21-29] of the twelve studies that we included for data extraction reported the inverse correlation of vitamin D levels with the stage of liver fibrosis in patients with CHC. Vitamin D has anti-inflammatory, anti-proliferative and anti-fibrotic effects that dampen inflammatory cell recruitment to the liver and mitigate hepatic fibrosis progression[40]. HCV may also have its own direct actions that impair vitamin D activity and status. It has been hypothesized that HCV affects 25-hydroxylation of vitamin D through cytokine induction or oxidative stress or through disruption in lipid metabolism where HCV suppress 25(OH)D levels due to a decrease in the production of vitamin D precursor, 7-dehydrocholesterol[10].

The profound relationship of vitamin D to immunity and inflammation, and our findings raise questions about how vitamin D status may impact the outcome of the many non-HCV chronic liver diseases. Individuals with chronic liver disease have significant global prevalence, morbidity, poor quality of life and mortality. Prior works have demonstrated adverse survival outcomes in patients with lowered vitamin D status[41,42]. In our analyses, we excluded papers reporting the analysis of vitamin D in chronic liver diseases other than HCV including chronic hepatitis B (CHB) which has a higher global prevalence of approximately 300 million infected individuals. Yu *et al*[43] evaluated the potential association between serum vitamin D level and liver histology or virological parameters in treatment-naïve patients with chronic hepatitis B infection in Southern China. They reported that patients infected with genotype B had a higher prevalence of vitamin D insufficiency than individuals with CHC. Furthermore, in chronic hepatitis B patients, serum 25(OH) D was not correlated with viral load or fibrosis. Mi *et al*[44] reported that vitamin D status was not different among Asians with non-cirrhotic CHB and CHC.

Low vitamin D status is associated with the risk of progression and the severity of hepatic inflammation in patients with non-alcoholic fatty liver disease[45,46]. Primary biliary cirrhosis has been extensively analyzed for correlations of vitamin D status predicting the outcome to ursodeoxycholic acid (UCDA) therapy and the influence of vitamin D supplementation to UCDA intervention[47-49]. Autoimmune hepatitis (AIH) has also been studied for the potential influence of vitamin D given the epidemiological association of this hormone with a number of diseases with autoimmunity[50,51]. However, there are not sufficient studies to draw meaningful conclusions of serum 25(OH)D and AIH at this time.

Altered vitamin D physiology *via* resistance from genetic polymorphisms of the vitamin D receptor (VDR) could also influence the outcome of CHC. Baur *et al*[25] demonstrated that low 25(OH)D plasma levels and VDR bAt[CCA]haplotype were associated with rapid fibrosis progression in CHC, separately and synergistic when co-present. Petta *et al*[52] reported that low hepatic VDR expression was inversely related to the severity of advanced liver fibrosis in patients with genotype 1 cCHC patients. Grunhage reported that a single nucleotide polymorphism (SNP) linked to the *DHCR7* gene coding vitamin D precursor dehydrocholesterol was related to altered serum 25(OH)D in chronic liver disease patients with no or mild fibrosis[53].

CHC with severely low vitamin D status is accompanied by advanced liver fibrosis. Interventional trials aimed to normalize vitamin D status in early stages of CHC may shed light on whether correction of vitamin D status in this patient population should become the standard of care.

COMMENTS

Background

Hepatitis C remains a global health burden affecting over 100 million people worldwide. There is growing evidence that vitamin D is inversely associated with liver inflammation and fibrosis in patients with chronic hepatitis C.

Research frontiers

Currently hepatitis C is being dramatically eradicated with DAA therapy. Possible augmentation of DAA therapy by vitamin D in those patients who already have fibrosis may decrease long term damage in the liver parenchyma.

Innovations and breakthroughs

The pooled data of this systematic review showed that 9 of the 12 studies correlated advanced liver disease defined as a Metavir value of F3/4 with 25(OH) D level insufficiency. The meta-analysis indicated a significant association across studies. Low vitamin D status is common in chronic Hepatitis C patients and is associated with advanced liver fibrosis.

Applications

Augmentation of standard hepatitis C therapy of direct acting antiviral meds with vitamin D may assist with long term decrease in liver fibrosis.

Peer-review

This is a very interesting and informative paper, and it deserves publication.

REFERENCES

1 **Lanini S**, Easterbrook PJ, Zumla A, Ippolito G. Hepatitis C: global epidemiology and strategies for control. *Clin Microbiol Infect* 2016; **22**: 833-838 [PMID: 27521803 DOI: 10.1016/j.cmi.2016.07.035]

2 **Shin EC**, Sung PS, Park SH. Immune responses and immunopathology in acute and chronic viral hepatitis. *Nat Rev Immunol* 2016; **16**: 509-523 [PMID: 27374637 DOI: 10.1038/nri.2016.69]

3 **Kim WR,** Smith JM, Skeans MA, Schladt DP, Schnitzler MA, Edwards EB, Harper AM, Wainright JL, Snyder JJ, Israni AK, Kasiske BL. OPTN/SRTR 2012 Annual Data Report: liver. *Am J Transplant* 2014; **14** Suppl 1: 69-96 [PMID: 24373168 DOI: 10.1111/ajt.12581]

4 **Sebastiani G**, Gkouvatsos K, Pantopoulos K. Chronic hepatitis C and liver fibrosis. *World J Gastroenterol* 2014; **20**: 11033-11053 [PMID: 25170193 DOI: 10.3748/wjg.v20.i32.11033]

5 **Poynard T**, Yuen MF, Ratziu V, Lai CL. Viral hepatitis C. *Lancet* 2003; **362** (9401): 2095-2100 [PMID: 14697814]

6 **Mullin GE**, Dobs A. Vitamin d and its role in cancer and immunity: a prescription for sunlight. *Nutr Clin Pract* 2007; **22**: 305-322 [PMID: 17507731]

7 **DeLuca HF**. Vitamin D: Historical Overview. *Vitam Horm* 2016; **100**: 1-20 [PMID: 26827946 DOI: 10.1016/bs.vh.2015.11.001]

8 **Pludowski P,** Holick MF, Pilz S, Wagner CL, Hollis BW, Grant WB, Shoenfeld Y, Lerchbaum E, Llewellyn DJ, Kienreich K, Soni M. Vitamin D effects on musculoskeletal health, immunity, autoimmunity, cardiovascular disease, cancer, fertility, pregnancy, dementia and mortality-a review of recent evidence. *Autoimmun Rev* 2013; **12**: 976-989 [PMID: 23542507 DOI: 10.1016/j.autrev.2013.02.004]

9 **Gatti D**, Idolazzi L, Fassio A. Vitamin D: not just bone, but also immunity. *Minerva Med* 2016; **107**: 452-460 [PMID: 27441391]

10 **Iruzubieta P**, Teran A, Crespo J, Fabrega E. Vitamin D deficiency in chronic liver disease. *World J Hepatol* 2014; **6**: 901-915 [PMID: 25544877 DOI: 10.4254/wjh.v6.i12.901]

11 **Peterlik M,** Cross HS. Vitamin D and calcium deficits predispose for multiple chronic diseases. *Eur J Clin Invest* 2005; **35**: 290-304 [PMID: 15860041 DOI: 10.1111/j.1365-2362.2005.01487.x]

12 **Feldman D**, Krishnan AV, Swami S, Giovannucci E, Feldman BJ. The role of vitamin D in reducing cancer risk and progression. *Nat Rev Cancer* 2014; **14**: 342-357 [PMID: 24705652 DOI: 10.1038/nrc3691]

13 **Luo YQ,** Wu XX, Ling ZX, Cheng YW, Yuan L, Xiang C. Association between serum vitamin D and severity of liver fibrosis in chronic hepatitis C patients: a systematic meta-analysis. *Zhejiang Daxue Xuebao Zirankexueban* 2014; **15**: 900-906 [DOI: 10.1631/jzus.B1400073]

14 **Hutton B**, Salanti G, Caldwell DM, Chaimani A, Schmid CH, Cameron C, Ioannidis JP, Straus S, Thorlund K, Jansen JP, Mulrow C, Catalá-López F, Gøtzsche PC, Dickersin K, Boutron I, Altman DG, Moher D. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. *Ann Intern Med* 2015; **162**: 777-784 [PMID: 26030634 DOI: 10.7326/M14-2385]

15 Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. In: Higgins JPT GSe, ed: The Cochrane Collaboration; 2011. Available from: URL: http://handbook.cochrane.org

16 **Balshem H**, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, Guyatt GH. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol* 2011; **64**: 401-406 [PMID: 21208779 DOI: 10.1016/j.jclinepi.2010.07.015]

17 **McClave SA,** DiBaise JK, Mullin GE, Martindale RG. ACG Clinical Guideline: Nutrition Therapy in the Adult Hospitalized Patient. *Am J Gastroenterol* 2016; **111**: 315-334; quiz 335 [PMID: 26952578 DOI: 10.1038/ajg.2016.28]

18 **Team RC**. A language and environment for statistical computing. R Foundation for Statistical Computing 2016 [DOI: 10.1007/s10985-007-9065-x]

19 **Viechtbauer W**. Conducting meta-analyses in R with the metafor package. *J Statistical Software* 2010; **36**: 1-48 [DOI: 10.18637/jss.v036.i03]

20 **El-Maouche D**, Mehta SH, Sutcliffe CG, Higgins Y, Torbenson MS, Moore RD, Thomas DL, Sulkowski MS, Brown TT. Vitamin D deficiency and its relation to bone mineral density and liver fibrosis in HIV-HCV coinfection. *Antiv Ther* 2013; **18**: 237-242 [DOI: 10.3851/IMP2264]

21 **Guzmán-Fulgencio M**, García-Álvarez M, Berenguer J, Jiménez-Sousa MÁ, Cosín J, Pineda-Tenor D, Carrero A, Aldámiz T, Alvarez E, López JC, Resino S. Vitamin D deficiency is associated with severity of liver disease in HIV/HCV coinfected patients. *J Infect* 2014; **68**: 176-184 [PMID: 24184809 DOI: 10.1016/j.jinf.2013.10.011]

22 **Terrier B**, Carrat F, Geri G, Pol S, Piroth L, Halfon P, Poynard T, Souberbielle JC, Cacoub P. Low 25-OH vitamin D serum levels correlate with severe fibrosis in HIV-HCV co-infected patients with chronic hepatitis. *J Hepatol* 2011; **55**: 756-761 [PMID: 21334402 DOI: 10.1016/j.jhep.2011.01.041]

23 **Lange CM**, Bibert S, Kutalik Z, Burgisser P, Cerny A, Dufour JF, Geier A, Gerlach TJ, Heim MH, Malinverni R, Negro F, Regenass S, Badenhoop K, Bojunga J, Sarrazin C, Zeuzem S, Müller T, Berg T, Bochud PY, Moradpour D. A genetic validation study reveals a role of vitamin D metabolism in the response to interferon-alfa-based therapy of chronic hepatitis C. *PLoS One* 2012; **7**: e40159 [PMID: 22808108 DOI: 10.1371/journal.pone.0040159]

24 **Weintraub SJ**, Fleckenstein JF, Marion TN, Madey MA, Mahmoudi TM, Schechtman KB. Vitamin D and the racial difference in the genotype 1 chronic hepatitis C treatment response. *Am J Clin Nutr* 2012; **96**: 1025-1031 [PMID: 23015322 DOI: 10.3945/ajcn.112.039974]

25 **Baur K**, Mertens JC, Schmitt J, Iwata R, Stieger B, Eloranta JJ, Frei P,

Stickel F, Dill MT, Seifert B, Ferrari HA, von Eckardstein A, Bochud PY, Müllhaupt B, Geier A. Combined effect of 25-OH vitamin D plasma levels and genetic vitamin D receptor (NR 1I1) variants on fibrosis progression rate in HCV patients. *Liver Int* 2012; **32**: 635-643 [PMID: 22151003 DOI: 10.1111/j.1478-3231.2011.02674.x]

26 **Mandorfer M**, Reiberger T, Payer BA, Ferlitsch A, Breitenecker F, Aichelburg MC, Obermayer-Pietsch B, Rieger A, Trauner M, Peck-Radosavljevic M. Low vitamin D levels are associated with impaired virologic response to PEGIFN+RBV therapy in HIV-hepatitis C virus coinfected patients. *AIDS* 2013; **27**: 227-232 [PMID: 23238552 DOI: 10.1097/QAD.0b013e32835aa161]

27 **Amanzada A**, Goralczyk AD, Moriconi F, van Thiel DH, Ramadori G, Mihm S. Vitamin D status and serum ferritin concentration in chronic hepatitis C virus type 1 infection. *J Med Virol* 2013; **85**: 1534-1541 [PMID: 23852677 DOI: 10.1002/jmv.23632]

28 **Gerova DI**, Galunska BT, Ivanova II, Kotzev IA, Tchervenkov TG, Balev SP, Svinarov DA. Prevalence of vitamin D deficiency and insufficiency in Bulgarian patients with chronic hepatitis C viral infection. *Scand J Clin Lab Invest* 2014; **74**: 665-672 [PMID: 25005344 DOI: 10.3109/00365513.2014.930710]

29 **Petta S**, Cammà C, Scazzone C, Tripodo C, Di Marco V, Bono A, Cabibi D, Licata G, Porcasi R, Marchesini G, Craxí A. Low vitamin D serum level is related to severe fibrosis and low responsiveness to interferon-based therapy in genotype 1 chronic hepatitis C. *Hepatology* 2010; **51**: 1158-1167 [PMID: 20162613 DOI: 10.1002/hep.23489]

30 **Abbasi HA**, Mozaffari HM, Esmaeilzadeh A, Mosannen mozaffari HM, Bahari A, Rezayat KA, Ghanaei O, Ganji A, Mokhtarifar A, Goshayeshi L. Association between Vitamin D deficiency and the severity of chronic liver disease and liver cirrhosis: Systematic literature review. *Govaresh* 2016; **21**: 64-71

31 **García-Álvarez M**, Pineda-Tenor D, Jiménez-Sousa MA, Fernández-Rodríguez A, Guzmán-Fulgencio M, Resino S. Relationship of vitamin D status with advanced liver fibrosis and response to hepatitis C virus therapy: a meta-analysis. *Hepatology* 2014; **60**: 1541-1550 [PMID: 24975775 DOI: 10.1002/hep.27281]

32 **Lange CM**, Bibert S, Kutalik Z. A large-scale genetic validation study coupled with in-vitro analyses reveal a role of vitamin d-signaling in the pathogenesis and treatment of chronic hepatitis C. *J Hepatol* 2011; **54**: S537

33 **Kitson MT**, Button P, Roberts SK. Reply to: "Vitamin D status does not predict sustained virologic response or fibrosis stage in chronic hepatitis C genotype 1 infection". *J Hepatology* 2013; **59**: 194-195 [DOI: 10.20524/aog.2016.0037]

34 **Esmat G**, El Raziky M, Elsharkawy A, Sabry D, Hassany M, Ahmed A, Assem N, El Kassas M, Doss W. Impact of vitamin D supplementation on sustained virological response in chronic hepatitis C genotype 4 patients treated by pegylated interferon/ribavirin. *J Interferon Cytokine Res* 2015; **35**: 49-54 [PMID: 25061714 DOI: 10.1089/jir.2014.0060]

35 **Forrest KY**, Stuhldreher WL. Prevalence and correlates of vitamin D deficiency in US adults. *Nutr Res* 2011; **31**: 48-54 [PMID: 21310306 DOI: 10.1016/j.nutres.2010.12.001]

36 **Ross AC**, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, Durazo-Arvizu RA, Gallagher JC, Gallo RL, Jones G, Kovacs CS, Mayne ST, Rosen CJ, Shapses SA. The 2011 Dietary Reference Intakes for Calcium and Vitamin D: what dietetics practitioners need to know. *J Am Diet Assoc* 2011; **111**: 524-527 [PMID: 21443983 DOI: 10.1016/j.jada.2011.01.004]

37 **Ross AC**. The 2011 report on dietary reference intakes for calcium and vitamin D. *Public Health Nutr* 2011; **14**: 938-939 [PMID: 21492489 DOI: 10.1017/S1368980011000565]

38 **Kitson MT**, Dore GJ, George J, Button P, McCaughan GW, Crawford DH, Sievert W, Weltman MD, Cheng WS, Roberts SK. Vitamin D status does not predict sustained virologic response or fibrosis stage in chronic hepatitis C genotype 1 infection. *J Hepatol* 2013; **58**: 467-472 [PMID: 23183524 DOI: 10.1016/j.jhep.2012.11.017]

39 **Nagpal S,** Na S, Rathnachalam R. Noncalcemic actions of vitamin D receptor ligands. *Endocr Rev* 2005; **26**: 662-687 [PMID: 15798098 DOI: 10.1210/er.2004-0002]

40 **Rahman AH**, Branch AD. Vitamin D for your patients with chronic hepatitis C? *J Hepatol* 2013; **58**: 184-189 [PMID: 22871501 DOI: 10.1016/j.jhep.2012.07.026]

41 **Finkelmeier F**, Kronenberger B, Zeuzem S, Piiper A, Waidmann O. Severe 25-hydroxyvitamin D deficiency is associated with infections and mortality in cirrhosis. *J Hepatol* 2015; **62**: S377-S378

42 **Grünhage F,** Mahler M, Reichel C, Lammert F. Extremely low vitamin d levels are associated with increased mortality in patients with liver cirrhosis. *J Hepatol* 2012; **56**: S247 [PMID: 24236541 DOI: 10.1111/eci.12205]

43 **Yu R**, Sun J, Zheng Z, Chen J, Fan R, Liang X, Zhu Y, Liu Y, Shen S, Hou J. Association between vitamin D level and viral load or fibrosis stage in chronic hepatitis B patients from Southern China. *J Gastroenterol Hepatol* 2015; **30**: 566-574 [PMID: 25238258 DOI: 10.1111/jgh.12783]

44 **Mi LJ,** Rincon-Bejarano LA, Babbar R. Vitamin d deficiency in Asian-American patients with chronic hepatitis B in New York downtown hospital. *Hepatology* 2011; **54**: 614A

45 **Nelson JE**, Roth CL, Wilson LA, Yates KP, Aouizerat B, Morgan-Stevenson V, Whalen E, Hoofnagle A, Mason M, Gersuk V, Yeh MM, Kowdley KV. Vitamin D Deficiency Is Associated with Increased Risk of Non-alcoholic Steatohepatitis in Adults with Non-alcoholic Fatty Liver Disease: Possible Role for MAPK and NF-kappaB? *Am J Gastroenterol* 2016; **111**: 852-863 [PMID: 27002799 DOI: 10.1038/ajg.2016.51]

46 **Eliades M**, Spyrou E. Vitamin D: A new player in non-alcoholic fatty liver disease? *World J Gastroenterol* 2015; **21**: 1718-1727 [PMID: 25684936 DOI: 10.3748/wjg.v21.i6.1718]

47 **Zhou X,** Guo G, Wang L, Shi Y, Han Y. Vitamin D supplementation therapy for primary biliary cirrhosis: A retrospective clinical study. *Hepatol Inter* 2016; **10**: S492-S493 [DOI: 10.1016/S0168-8278(16)01219-8]

48 **Guo GY**, Shi YQ, Wang L, Ren X, Han ZY, Guo CC, Cui LN, Wang JB, Zhu J, Wang N, Zhang J, Cai Y, Han Y, Zhou XM, Fan DM. Serum vitamin D level is associated with disease severity and response to ursodeoxycholic acid in primary biliary cirrhosis. *Aliment Pharmacol Ther* 2015; **42**: 221-230 [PMID: 25982180 DOI: 10.1111/apt.13244]

49 **Agmon-Levin N**, Kopilov R, Selmi C, Nussinovitch U, Sánchez-Castañón M, López-Hoyos M, Amital H, Kivity S, Gershwin EM, Shoenfeld Y. Vitamin D in primary biliary cirrhosis, a plausible marker of advanced disease. *Immunol Res* 2015; **61**: 141-146 [PMID: 25424577 DOI: 10.1007/s12026-014-8594-0]

50 **Efe C**, Kav T, Aydin C, Cengiz M, Imga NN, Purnak T, Smyk DS, Torgutalp M, Turhan T, Ozenirler S, Ozaslan E, Bogdanos DP. Low serum vitamin D levels are associated with severe histological features and poor response to therapy in patients with autoimmune hepatitis. *Hepatol Inter* 2015; **9**: S130

51 **Efe C**, Kav T, Aydin C, Kav T, Aydin C, Cengiz M, Imga NN, Purnak T, Smyk DS, Torgutalp M, Turhan T, Ozenirler S, Ozaslan E, Bogdanos DP. Low serum vitamin D levels are associated with severe histological features and poor response to therapy in patients with autoimmune hepatitis. *Dig Dis Sci* 2014; **59**: 3035-3042 [PMID: 25002309 DOI: 10.1007/s10620-014-3267-3]

52 **Petta S,** Grimaudo S, Tripodo C, Cabibi D, Calvaruso M, Di Cristina A, Guarnotta C, Macaluso FS, Minissale MG, Marchesini G, Craxì A. The hepatic expression of vitamin D receptor is inversely associated with the severity of liver damage in genotype 1 chronic hepatitis C patients. *J Clin Endocrinol Metab* 2013; **100**: 193-200 [PMID: 25268393 DOI: 10.1210/jc.2014-2741]

53 **Grünhage F**, Hochrath K, Krawczyk M, Höblinger A, Obermayer-Pietsch B, Geisel J, Trauner M, Sauerbruch T, Lammert F. Common genetic variation in vitamin D metabolism is associated with liver stiffness. *Hepatology* 2012; **56**: 1883-1891 [PMID: 22576297 DOI: 10.1002/hep.25830]

54 **Parian AM**, Limketkai BN, Shah ND, Mullin GE. Nutraceutical Supplements for Inflammatory Bowel Disease. *Nutr Clin Pract* 2015; **30**: 551-558 [PMID: 26024677 DOI: 10.1177/0884533615586598]

55 **Mullin GE.** Micronutrients and inflammatory bowel disease. *Nutr Clin Pract* 2012; **27**: 136-137 [PMID: 22223669 DOI: 10.1177/0884533611433436]
56 **Mullin GE**, Turnbull LK, Kines K. Vitamin D: a D-lightful health supplement: part II. *Nutr Clin Pract* 2009; **24**: 738-740 [PMID: 19955553 DOI: 10.1177/0884533609351534]
57 **Mullin GE**, Turnbull L, Kines K. Vitamin D: a D-lightful health supplement. *Nutr Clin Pract* 2009; **24**: 642-644 [PMID: 19841251 DOI: 10.1177/0884533609343938]
58 **Clarke JO**, Mullin GE. A review of complementary and alternative approaches to immunomodulation. *Nutr Clin Pract* 2008; **23**: 49-62 [PMID: 18203964 DOI: 10.1177/011542650802300149]

P- Reviewer: El-Bendary MM, Ferraioli G, Ramsay MA, Wong GLH
S- Editor: Qi Y **L- Editor**: A **E- Editor**: Li D

World Journal of Hepatology

Submit a Manuscript: http://www.wjgnet.com/esps/

DOI: 10.4254/wjh.v9.i5.288

World J Hepatol 2017 February 18; 9(5): 288-292

ISSN 1948-5182 (online)

META-ANALYSIS

Is it time to rethink combined liver-kidney transplant in hepatitis C patients with advanced fibrosis?

Niraj James Shah, Mark W Russo

Niraj James Shah, Department of Medicine, Division of Digestive Diseases, the University of Mississippi Medical Center, Jackson, MS 39216, United States

Mark W Russo, Transplant Center-Carolinas Medical Center, 6th Floor Morehead Medical Plaza, Charlotte, NC 28024, United States

Author contributions: Both the authors contributed to the manuscript.

Conflict-of-interest statement: The authors declare no conflicts of interest regarding this manuscript.

Data sharing statement: No additional data are available.

Manuscript source: Unsolicited manuscript

Correspondence to: Niraj James Shah, MD, Assistant Professor of Medicine, Department of Medicine, Division of Digestive Diseases, the University of Mississippi Medical Center, 2500 North State Street, Jackson, MS 39216, United States. jnshah@umc.edu
Telephone: +1-601-9844540
Fax: +1-601-9844548

Received: September 27, 2016
Peer-review started: September 28, 2016
First decision: October 31, 2016
Revised: December 4, 2016
Accepted: December 16, 2016
Article in press: December 19, 2016
Published online: February 18, 2017

Abstract

AIM

To reduce hepatic and extrahepatic complications of chronic hepatitis C in kidney transplant recipients.

METHODS

We conducted a systematic review of kidney only transplant in patients with hepatitis C and advanced fibrosis.

RESULTS

The 5 year patient survival of kidney transplant recipients with and without hepatitis C cirrhosis ranged from 31% to 90% and 85% to 92%, respectively. Hepatitis C kidney transplant recipients had lower 10-year survival when compared to hepatitis B patients, 40% and 90% respectively. There were no studies that included patients with virologic cure prior to kidney transplant that reported post-kidney transplant outcomes. There were no studies of direct acting antiviral therapy and effect on patient or graft survival after kidney transplantation.

CONCLUSION

Data on kidney transplant only in hepatitis C patients that reported inferior outcomes were prior to the development of potent direct acting antiviral. With the development of potent directing acting antiviral therapy for hepatitis C with high cure rates studies are needed to determine if patients with hepatitis C, including those with advanced fibrosis, can undergo kidney transplant alone with acceptable long term outcomes.

Key words: Cirrhosis/cirrhotics; Renal transplantation; Kidney transplantation; Mortality; Systematic review; Graft outcomes; Meta-analysis

Core tip: Individuals with chronic hepatitis C with advanced fibrosis and kidney failure who undergo kidney transplant alone are believed to have lower long-term survival. Surprisingly, we have only a few studies with inconsistent results. The concern about isolated-kidney-transplant alone is that the liver disease would progress to decompensated cirrhosis and liver failure in the setting of immunosuppression after kidney transplant. Earlier, interferon was associated with low virologic cure and high adverse events including graft rejection. However, with development of newer directly acting anti-virals we wish to invite our readers to reconsider the need for a combined liver-kidney transplant in hepatitis C patients with advanced fibrosis or compensated cirrhosis.

Shah NJ, Russo MW. Is it time to rethink combined liver-kidney transplant in hepatitis C patients with advanced fibrosis? *World J Hepatol* 2017; 9(5): 288-292 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i5/288.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i5.288

INTRODUCTION

Patients with hepatitis C virus (HCV) cirrhosis undergoing kidney transplantation only have lower post-transplant survival rates compared to recipients without hepatitis C or cirrhosis[1]. After the implementation of the model for end-stage liver disease (MELD) scoring system for allocating liver transplants, the number of simultaneous liver-kidney transplantation has increased by 300%[2]. Some of these patients may have relatively well compensated cirrhosis and patients with well compensated cirrhosis but kidney failure may receive a MELD score of 20 based upon a creatinine of 4 mg/dL. These patients may have compensated cirrhosis without complications of portal hypertension. Thus, kidney failure, not liver failure may be the driving factor for priority for liver transplant in this subgroup. This is particularly relevant in areas of the country where patients may receive liver transplants at relatively low MELD scores compared to areas with higher demand.

The reason for dual listing patients with hepatitis C cirrhosis and kidney failure who may be well compensated is the concern of decompensation after liver-kidney transplant. Immunosuppressive therapy to prevent rejection increases the titers of HCV RNA and immunosuppression has been associated with accelerated hepatitis injury such as fibrosing cholestatic hepatitis C[3]. However, the impact on treating and curing candidates before or after kidney transplant has not been well studied. The high virologic cure rates may have important implications for patients in kidney failure with hepatitis C and advanced liver fibrosis.

The guidelines for liver kidney transplant are conflicting or without detailed recommendations. The AASLD and KDIGO guidelines do not directly address the issue of isolated kidney transplant in the setting of cirrhosis or advanced liver fibrosis. The EASL guidelines state that patients with established cirrhosis and portal hypertension who fail (or are unsuitable for) HCV antiviral treatment, isolated renal transplantation may be contra-indicated and consideration should be given to combined liver and kidney transplantation[4]. Patients with symptomatic or presence of portal hypertension are considered candidates for kidney-liver transplantation[2]. There is no consensus for patients with hepatitis C and periportal fibrosis or bridging fibrosis who are kidney transplant candidates.

The aim of this systematic review was to assess the outcome of hepatitis C cirrhotics undergoing kidney only transplant and suggest areas for further study in patients with hepatitis C and advanced fibrosis who are kidney transplant candidates.

MATERIALS AND METHODS

Literature search

We conducted online electronic searches (published human clinic trials in English) of the National Library of Medicine's (Bethesda, MD, United States) MEDLINE database, Cochrane Library and manual searches of selected specialty journals to identify any pertinent literature. Three MEDLINE database engines (Ovid, PubMed and EMBASE) were searched using the key words "cirrhosis", "cirrhotics", "chronic hepatitis C", "renal transplantation", "kidney transplantation", "mortality", "graft outcomes". The references of articles were reviewed for additional articles.

Inclusion criteria

Clinical studies (prospective and retrospective) from the last 20 years on kidney transplant recipients with HCV cirrhosis (both compensated and decompensated) were included. The studies required a minimum of a 1 year post transplant follow-up with information regarding graft and patient survival outcomes.

Exclusion criteria

Studies not published in English or published only in the abstract form were excluded.

Primary end point

To compare post kidney transplant survival in hepatitis C cirrhotics undergoing kidney transplant alone to recipients without hepatitis C and without cirrhosis.

Source of support

This systematic review was not supported by any pharmaceutical company, governmental agency or other grants.

RESULTS

Figure 1 shows studies[5-9] in patients with hepatitis C

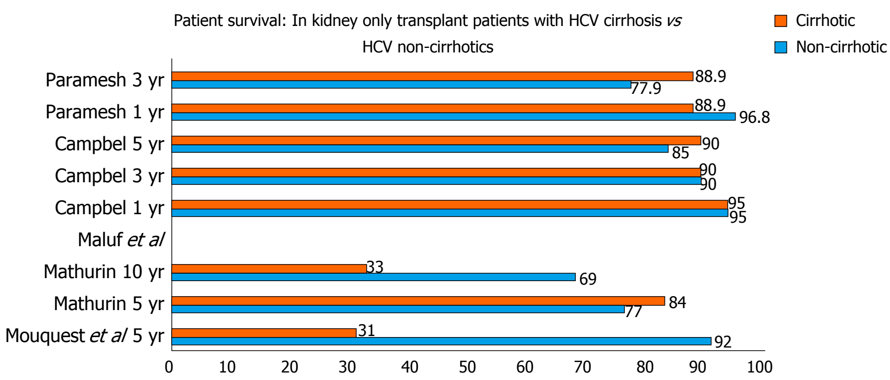

Figure 1 Studies in patients with hepatitis C who underwent kidney transplant only. HCV: Hepatitis C virus.

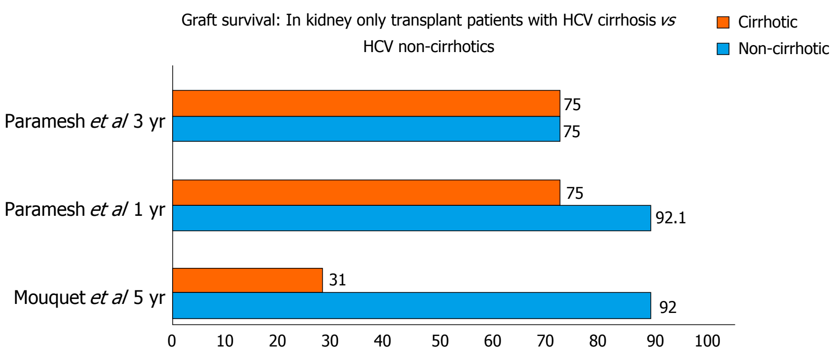

Figure 2 Graft survival in kidney only transplant patients. HCV: Hepatitis C virus.

who underwent kidney transplant only. Five studies were identified that included 2511 patients. Of these 2511 patients, 458 had hepatitis C while 69 were confirmed to have cirrhosis based on a liver biopsy. The mean age ranged from 35 to 57 years with a male to female ratio of 1.73:1. The study by Mathurin *et al*[6] consisted of 66% Europeans and 31% Africans, while in most of the other studies 66%-79% of the study population was African-American. The most common etiology of kidney disease was diabetes mellitus. Only one study provided the mean MELD score (20.6)[9]. Data on hepatitis C genotyping was not reported in any study. In all the studies the donors were deceased donors. One patient in the Mouquet *et al*[5] study was coinfected with hepatitis B. Two studies reported the specific immunosuppressive regimen with either cyclosporine or tacrolimus.

Outcomes of studies

The studies reported either 1, 3, 5 or 10 year survival of HCV cirrhotics *vs* non-cirrhotics. One year and three year survival were available for 3 studies. The 1-year and 3-year patient survival was 88.9% to 95% and 37% to 90% in cirrhotics *vs* 95% to 96.3% and 76% to 90% in non-cirrhotics. The 5-year and 10-year graft survival was 31%-90% and 33% ± 11% in cirrhotics when compared to 85%-92% and 69% ± 7% in non-cirrhotics.

Mathurin *et al*[6] reported that the presence of cirrhosis (P = 0.02) and HbsAg positive status (P < 0.0001) were associated with poor 5 and 10-year survival, 84% ± 7% and 33% ± 11%, respectively. Maluf *et al*[7] demonstrated the Knodell histology score was associated with mortality in hepatitis C kidney transplant patients (P = 0.012).

The study by Campbell *et al*[8] reported that survival after kidney transplant only in recipients with hepatitis C was similar between patients with minimal liver fibrosis compared to patients with advanced fibrosis. Paramesh *et al*[9] reported kidney transplant alone to be safe in compensated hepatitis C cirrhosis; HR = 1.4, P = 0.7817 compared to graft survival in non-cirrhotics: HR = 0.81, P = 0.758) (Figure 2).

DISCUSSION

Individuals with chronic hepatitis C with advanced fibrosis and kidney failure who undergo kidney transplant alone are believed to have lower long term survival although there are surprisingly few studies on this patient population. Furthermore, there has not been consistent results among studies reporting outcomes of isolated kidney transplant in hepatitis C infected recipients. The concern about isolated kidney transplant alone in a patients with hepatitis C and advanced liver fibrosis is that the liver disease will progress to decompensated cirrhosis and liver failure in the setting of immunosuppression after kidney transplant. The progression of liver disease from hepatitis C after kidney transplant was of particular concern during the interferon era because of limited therapy for hepatitis C. Interferon is associated with low virologic cure and high adverse events including graft rejection. However, with the development of interferon free regimens and direct acting antiviral agents the need of combined liver-kidney transplant in hepatitis C patients who have hepatitis C and advanced fibrosis or compensated cirrhosis needs to be readdressed.

Patients with cirrhosis after kidney transplant may be at a greater risk of immune dysfunction and developing lethal infections because patients with cirrhosis have multiple immunological defects. Cirrhotic patients have reduced cell-mediated immunity[10,11] reduced neutrophil phagocytic ability[12] and impaired macrophage Fc receptor function[13]. In the setting of immunosuppression the risk of infection in patients with cirrhosis is likely higher than without immunosuppression. However, if liver fibrosis regresses then the risk of infection may be reduced. In a 10-year study following 51 kidney transplant recipients with hepatitis C who underwent serial liver biopsies, Kamar *et al*[14] showed that HCV infection was not associated with worsening liver histology in 50% of patients. Furthermore, there may be regression of liver fibrosis in some patients after kidney transplantation[15]. In fact, Paramesh *et al*[9] concluded that the presence of cirrhosis in HCV-positive patients is not a significant variable affecting either graft or patient survival.

One strategy is to of treat all chronic hepatitis C patients with direct acting antiviral therapy while waiting for kidney transplant. The regimens that are currently available include sofosbuvir/ledipasvir, sofosbuvir/daclatasvir, and paritaprevir/ritonavir/ombitasvir/dasabuvir. Each of these regimens may require the addition of ribavirin depending on patient characteristics such as genotype or presence of cirrhosis. Sofosbuvir is renally cleared and not indicated in patients with glomerular filtration rates less than 30 mL/min. Ribavirin is renally cleared and although there is renal dosing for ribavirin it may be associated with a 2-4 g/dL drop in hemoglobin which may not be tolerated in some patients with kidney failure. Thus, given these limitations many patients with kidney failure may not be candidates for therapy with the currently available direct acting antiviral agents. Paritaprevir/ritonavir/ombitasvir/dasabuvir has been studied in patients with hepatitis C and kidney failure with virologic cure rates exceeding 85%[16]. There are other direct acting antiviral agents in development for hepatitis C patients with kidney failure that will provide additional treatment options for this patient population.

During the era of interferon based regimens for hepatitis C high rates of rejection in kidney transplant recipients was reported. Rejection rates of 40%-60% were reported with interferon based regimens with rare cases of graft loss[17-22]. The mechanism of rejection is believed to be the immune mediated injury from interferon. The direct-acting antiviral agents regimens are interferon free and due not stimulate the T cell response and should not be associated with rejection. The direct acting agents have been studied in liver transplant recipients with virologic cure exceeding 90% and acceptable safety profile with little or no rejection[23-27]. Although there is no theoretical reason to believe the direct acting antiviral agents would be associated with increased risk of kidney rejection this would be studied in clinical trials. Additional important findings from this review include the lack of reporting of relevant data related to hepatitis C including genotype, liver fibrosis, viral load and prior treatment history. Studies of hepatitis C in patients with kidney disease should systematically report these data in a standardized fashion. Furthermore, the number of subjects with hepatitis C and advanced fibrosis was small and it is likely a multicenter study will best demonstrate if there is any difference in outcomes between kidney transplant recipients without hepatitis, with hepatitis C and mild liver fibrosis, and hepatitis C and advanced fibrosis.

We suggest we should treat all chronic hepatitis C patients irrespective of the fibrotic staging; especially those that we anticipate may be on the waiting list for a longer time.

In conclusion, data are lacking or outdated on post renal transplant outcomes in recipients with chronic hepatitis C. There is no substantiated evidence on which to base a decision to perform kidney transplant alone or a kidney-liver transplantation in a patient with chronic hepatitis C and advanced fibrosis or well compensated cirrhosis. Given limited resources of organs data are sorely needed so evidence based decisions can be made on how best to allocate kidneys in patients with liver disease. The time has come to conduct a large multicenter trial in kidney transplant candidates and recipients with hepatitis C to determine how organs should best be allocated.

COMMENTS

Background

Individuals with chronic hepatitis C with advanced fibrosis and kidney failure who undergo kidney transplant alone are believed to have lower long-term survival. Surprisingly, the authors have only a few studies with inconsistent results. The concern about isolated-kidney-transplant alone is that the liver disease would progress to decompensated cirrhosis and liver failure in the setting of immunosuppression after kidney transplant.

Research frontiers

With further research on the use of direct-acting antiviral agents's (DAA's) in this subgroup of patients with hepatitis C virus (HCV) listed for renal transplant; the authors could come to a consensus to draft acceptable guidelines for better management of this subgroup of patients.

Innovations and breakthroughs

Earlier, interferon was associated with low virologic cure and high adverse events including graft rejection. This has been replaced by newer DAA's that are safe and potent with fewer side events.

Applications

The main objective is to invite hepatologist, transplant hepatologist and transplant nephrologist to consider DAA's in all HCV patients on the renal transplant list.

Terminology

DAA's: Directly acting anti-virals.

Peer-review

This is a correct, well-written review on the different autoimmune forms of liver disease, clinical manifestations and evolution, and treatment.

REFERENCES

1 **Rao KV**, Andersen RC. Long-term results and complications in renal transplant recipients. Observations in the second decade. *Transplantation* 1988; **45**: 45-52 [PMID: 3276061]
2 **Eason JD**, Gonwa TA, Davis CL, Sung RS, Gerber D, Bloom RD. Proceedings of Consensus Conference on Simultaneous Liver Kidney Transplantation (SLK). *Am J Transplant* 2008; **8**: 2243-2251 [PMID: 18808402 DOI: 10.1111/j.1600-6143.2008.02416.x]
3 **Narang TK**, Ahrens W, Russo MW. Post-liver transplant cholestatic hepatitis C: a systematic review of clinical and pathological findings and application of consensus criteria. *Liver Transpl* 2010; **16**: 1228-1235 [PMID: 21031537 DOI: 10.1002/lt.22175]
4 **Van Wagner LB**, Baker T, Ahya SN, Norvell JP, Wang E, Levitsky J. Outcomes of patients with hepatitis C undergoing simultaneous liver-kidney transplantation. *J Hepatol* 2009; **51**: 874-880 [PMID: 19643508 DOI: 10.1016/j.jhep.2009.05.025]
5 **Mouquet C**, Mathurin P, Sylla C, Benalia H, Opolon P, Coriat P, Bitker MO. Hepatic cirrhosis and kidney transplantation outcome. *Transplant Proc* 1997; **29**: 2406 [PMID: 9270783 DOI: 10.1016/S0041-1345(97)00422-3]
6 **Mathurin P**, Mouquet C, Poynard T, Sylla C, Benalia H, Fretz C, Thibault V, Cadranel JF, Bernard B, Opolon P, Coriat P, Bitker MO. Impact of hepatitis B and C virus on kidney transplantation outcome. *Hepatology* 1999; **29**: 257-263 [PMID: 9862875 DOI: 10.1002/hep.510290123]
7 **Maluf DG**, Fisher RA, King AL, Gibney EM, Mas VR, Cotterell AH, Shiffman ML, Sterling RK, Behnke M, Posner MP. Hepatitis C virus infection and kidney transplantation: predictors of patient and graft survival. *Transplantation* 2007; **83**: 853-857 [PMID: 17460555 DOI: 10.1097/01.tp.0000259725.96694.0a]
8 **Campbell MS**, Constantinescu S, Furth EE, Reddy KR, Bloom RD. Effects of hepatitis C-induced liver fibrosis on survival in kidney transplant candidates. *Dig Dis Sci* 2007; **52**: 2501-2507 [PMID: 17394069]
9 **Paramesh AS**, Davis JY, Mallikarjun C, Zhang R, Cannon R, Shores N, Killackey MT, McGee J, Saggi BH, Slakey DP, Balart L, Buell JF. Kidney transplantation alone in ESRD patients with hepatitis C cirrhosis. *Transplantation* 2012; **94**: 250-254 [PMID: 22790385 DOI: 10.1097/TP.0b013e318255f890]
10 **Morgan MY**, Mcintyre N. Nutritional aspects of liver disease in Liver and Biliary Disease: Pathophysiology, Diagnosis, Management. In: Wright R, Millward-Sadler G, Albert K, Karran S. London, 1985: 119
11 **Hsu CC**, Leevy CM. Inhibition of PHA-stimulated lymphocyte transformation by plasma from patients with advanced alcoholic cirrhosis. *Clin Exp Immunol* 1971; **8**: 749-760 [PMID: 5581064]
12 **Rajkovic IA**, Williams R. Abnormalities of neutrophil phagocytosis, intracellular killing and metabolic activity in alcoholic cirrhosis and hepatitis. *Hepatology* 1986; **6**: 252-262 [PMID: 3007318]
13 **Gomez F**, Ruiz P, Schreiber AD. Impaired function of macrophage Fc gamma receptors and bacterial infection in alcoholic cirrhosis. *N Engl J Med* 1994; **331**: 1122-1128 [PMID: 7935636 DOI: 10.1056/NEJM199410273311704]
14 **Kamar N**, Rostaing L, Selves J, Sandres-Saune K, Alric L, Durand D, Izopet J. Natural history of hepatitis C virus-related liver fibrosis after renal transplantation. *Am J Transplant* 2005; **5**: 1704-1712 [PMID: 15943629 DOI: 10.1111/j.1600-6143.2005.00918.x]
15 **Roth D**, Gaynor JJ, Reddy KR, Ciancio G, Sageshima J, Kupin W, Guerra G, Chen L, Burke GW. Effect of kidney transplantation on outcomes among patients with hepatitis C. *J Am Soc Nephrol* 2011; **22**: 1152-1160 [PMID: 21546575 DOI: 10.1681/ASN.2010060668]
16 **Pockros PJ**, Reddy KR, Mantry PS, Cohen E, Bennett M, Sulkowski MS, Bernstein DE, Cohen DE, Shulman NS, Wang D, Khatri A, Abunimeh M, Podsadecki T, Lawitz E. Efficacy of Direct-Acting Antiviral Combination for Patients With Hepatitis C Virus Genotype 1 Infection and Severe Renal Impairment or End-Stage Renal Disease. *Gastroenterology* 2016; **150**: 1590-1598 [PMID: 26976799 DOI: 10.1053/j.gastro.2016.02.078]
17 **Ozgür O**, Boyacioğlu S, Telatar H, Haberal M. Recombinant alpha-interferon in renal allograft recipients with chronic hepatitis C. *Nephrol Dial Transplant* 1995; **10**: 2104-2106 [PMID: 8643176]
18 **Harihara Y**, Kurooka Y, Yanagisawa T, Kuzuhara K, Otsubo O, Kumada H. Interferon therapy in renal allograft recipients with chronic hepatitis C. *Transplant Proc* 1994; **26**: 2075 [PMID: 8066675]
19 **Rostaing L**, Izopet J, Baron E, Duffaut M, Puel J, Durand D. Treatment of chronic hepatitis C with recombinant interferon alpha in kidney transplant recipients. *Transplantation* 1995; **59**: 1426-1431 [PMID: 7770930]
20 **Chan TM**, Lok AS, Cheng IK, Ng IO. Chronic hepatitis C after renal transplantation. Treatment with alpha-interferon. *Transplantation* 1993; **56**: 1095-1098 [PMID: 8249107]
21 **Fabrizi F**, Penatti A, Messa P, Martin P. Treatment of hepatitis C after kidney transplant: a pooled analysis of observational studies. *J Med Virol* 2014; **86**: 933-940 [PMID: 24610278 DOI: 10.1002/jmv.23919]
22 **Wei F**, Liu J, Liu F, Hu H, Ren H, Hu P. Interferon-based anti-viral therapy for hepatitis C virus infection after renal transplantation: an updated meta-analysis. *PLoS One* 2014; **9**: e90611 [PMID: 24699257 DOI: 10.1371/journal.pone.0090611]
23 **Charlton M**, Everson GT, Flamm SL, Kumar P, Landis C, Brown RS, Fried MW, Terrault NA, O'Leary JG, Vargas HE, Kuo A, Schiff E, Sulkowski MS, Gilroy R, Watt KD, Brown K, Kwo P, Pungpapong S, Korenblat KM, Muir AJ, Teperman L, Fontana RJ, Denning J, Arterburn S, Dvory-Sobol H, Brandt-Sarif T, Pang PS, McHutchison JG, Reddy KR, Afdhal N. Ledipasvir and Sofosbuvir Plus Ribavirin for Treatment of HCV Infection in Patients With Advanced Liver Disease. *Gastroenterology* 2015; **149**: 649-659 [PMID: 25985734 DOI: 10.1053/j.gastro.2015.05.010]
24 **Gutierrez JA**, Carrion AF, Avalos D, O'Brien C, Martin P, Bhamidimarri KR, Peyton A. Sofosbuvir and simeprevir for treatment of hepatitis C virus infection in liver transplant recipients. *Liver Transpl* 2015; **21**: 823-830 [PMID: 25825070 DOI: 10.1002/lt.24126]
25 **Pungpapong S**, Aqel B, Leise M, Werner KT, Murphy JL, Henry TM, Ryland K, Chervenak AE, Watt KD, Vargas HE, Keaveny AP. Multicenter experience using simeprevir and sofosbuvir with or without ribavirin to treat hepatitis C genotype 1 after liver transplant. *Hepatology* 2015; **61**: 1880-1886 [PMID: 25722203 DOI: 10.1002/hep.27770]
26 **Saab S**, Greenberg A, Li E, Bau SN, Durazo F, El-Kabany M, Han S, Busuttil RW. Sofosbuvir and simeprevir is effective for recurrent hepatitis C in liver transplant recipients. *Liver Int* 2015; **35**: 2442-2447 [PMID: 25913321]
27 **Kwo PY**, Mantry PS, Coakley E, Te HS, Vargas HE, Brown R, Gordon F, Levitsky J, Terrault NA, Burton JR, Xie W, Setze C, Badri P, Pilot-Matias T, Vilchez RA, Forns X. An interferon-free antiviral regimen for HCV after liver transplantation. *N Engl J Med* 2014; **371**: 2375-2382 [PMID: 25386767 DOI: 10.1056/NEJMoa1408921]

P- Reviewer: Ikuta S, Kapoor S, Sipos F **S- Editor**: Qiu S
L- Editor: A **E- Editor**: Li D

Baishideng®

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