

## Hepatitis C virus: A time for decisions. Who should be treated and when?

Bashar M Attar, David H Van Thiel

Bashar M Attar, Cook County Health and Hospitals System, Rush University Medical Center, Chicago, IL 60612, United States

David H Van Thiel, Advanced Liver and Gastrointestinal Disease Center, Berwyn, IL 60402, United States

**Author contributions:** Both the authors contribute to collect of data, synthesis, and write of the manuscript.

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

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Correspondence to:** Bashar M Attar, MD, PhD, MPH, Cook County Health and Hospitals System, Rush University Medical Center, 1901 West Harrison Street, Chicago, IL 60612, United States. [battar@rush.edu](mailto:battar@rush.edu)  
Telephone: +1-312-8647213  
Fax: +1-312-8649214

Received: June 24, 2015

Peer-review started: June 24, 2015

First decision: August 3, 2015

Revised: September 16, 2015

Accepted: November 13, 2015

Article in press: November 17, 2015

Published online: February 6, 2016

### Abstract

Cirrhosis is the most important risk factor for hepatocellular carcinoma (HCC) regardless of the etiology of cirrhosis. Compared to individuals who are anti-

hepatitis C virus (HCV) seronegative, anti-HCV seropositive individuals have a greater mortality from both hepatic as well as nonhepatic disease processes. The aim of this paper is to describe the burden of HCV infection and consider treatment strategies to reduce HCV-related morbidity and mortality. The newly developed direct acting antiviral (DAA) therapies are associated with greater rates of drug compliance, fewer adverse effects, and appear not to be limited by the presence of a variety of factors that adversely affect the outcome of interferon-based therapies. Because of the cost of the current DAA, their use has been severely rationed by insurers as well as state and federal agencies to those with advanced fibrotic liver disease (Metavir fibrosis stage F3-F4). The rationale for such rationing is that many of those recognized as having the disease progress slowly over many years and will not develop advanced liver disease manifested as chronic hepatitis C, cirrhosis, and experience any of the multiple complications of liver disease to include HCC. This mitigation has a short sided view of the cost of treatment of hepatitis C related disease processes and ignores the long-term expenses of hepatitis C treatment consisting of the cost of treatment of hepatitis C, the management of cirrhosis with or without decompensation as well as the cost of treatment of HCC and liver transplantation. We believe that treatment should include all HCV infected patients including those with stage F0-F2 fibrosis with or without evidence of coexisting liver disease. Specifically, interferon (IFN)-free regimens with the current effective DAAs without liver staging requirements and including those without evidence of hepatic diseases but having recognized extrahepatic manifestations of HCV infection is projected to be the most cost-effective approach for treating HCV in all of its varied presentations. Early rather than later therapy of HCV infected individuals would be even more efficacious than waiting particularly if it includes all cases from F0-F4 hepatic disease. Timely therapy will reduce the number of individuals developing advanced

liver disease, reduce the cost of treating these cases and more importantly, reduce the lifetime cost of treatment of those with any form of HCV related disease as well as HCV associated all-cause mortality. Importantly, HCV treatment regimens without any restrictions would result in a substantial reduction in health care expenditure and simultaneously reduce the number of infected individuals who are infecting others.

**Key words:** Hepatitis C virus; Direct acting antivirals; Cirrhosis of the liver; Timing of treatment

© **The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** This study presents the burden of hepatitis C virus (HCV) infection. Current guidelines limit treatment to those with advanced liver disease (Metavir F-3 or F-4 fibrosis). This represents a small fraction of those infected having the worse prognosis. They are unlikely to infect others. In contrast, the much larger group F-0 to F-2 is the vectors for additional infections. The plague of HCV can only be eliminated if the larger groups that infect others are treated. The cost of treating this larger population is expensive but much less expensive than treating only those with advanced fibrosis in the long run.

Attar BM, Van Thiel DH. Hepatitis C virus: A time for decisions. Who should be treated and when? *World J Gastrointest Pharmacol Ther* 2016; 7(1): 33-40 Available from: URL: <http://www.wjgnet.com/2150-5349/full/v7/i1/33.htm> DOI: <http://dx.doi.org/10.4292/wjgpt.v7.i1.33>

## INTRODUCTION

Chronic hepatitis C virus (HCV) infection is an important cause of advanced liver disease and liver-related deaths. The aim of this document is to describe the burden of HCV infection and consider treatment strategies to reduce HCV-related morbidity and mortality<sup>[1-5]</sup>.

It is estimated that the incidence of hepatocellular carcinoma (HCC) in Europe and United States will peak at 2020 at which there will be 78000 new HCC cases in Europe and 27000 in the United States<sup>[6]</sup>. Cirrhosis is the most important risk factor for HCC regardless of the etiology and cirrhosis occurs in the background of 90% of cases of HCC<sup>[6]</sup>.

These figures probably underestimate the actual prevalence of the disease HCV as they are based upon data that excludes groups at recognized highest risks for the infection. Despite these limitations relative to the current estimates of the disease prevalence, it is well recognized that 50%-85% of the patients infected with HCV and manifest a hepatic disease process develop a chronic hepatitis and 20%-25% of these cases progress to cirrhosis with 20% of this latter

group progressing further to HCC<sup>[7-9]</sup>.

## RISK OF HCV INFECTION AND NEED FOR SCREENING

HCV infection has an increasing HCV-related mortality from 1.09 to 2.40 per 100000 person years in the United States from 1995 to 2004<sup>[10]</sup>. The predicted mortality of HCV related disease over a 20-year period is expected to continue to rise as more and more individuals, who are currently infected, will have their disease for many more years. As a result, the healthcare burden in direct and indirect costs related to HCV infection will continue to rise in the foreseeable future<sup>[10]</sup>. The detection of HCV RNA in serum identifies active cases manifested by replication of the virus. Lee *et al*<sup>[10]</sup> reported that 52%-80% of serum samples seropositive for anti-HCV have been reported to have detectable serum levels of HCV RNA. Importantly, anti-HCV seropositive individuals with detectable serum HCV RNA have an increased risk of dying from all causes, whereas the risk for anti-HCV seropositives with negative HCV RNA is similar to that of HCV seronegative individuals<sup>[9,10]</sup>. Indeed, 2394 deaths occurred in HCV positive individuals during an average follow-up period of 16.2 years. Compared to individuals, who are anti-HCV seronegative, anti-HCV seropositive individuals have a greater mortality from both hepatic as well as nonhepatic disease processes. The multivariate-adjusted hazard ratio [95% confidence interval (CI)] of 1.89 (1.66-2.15) for all causes of death in HCV seropositive individuals and 12.48 (9.34-16.66) for hepatic diseases, 1.35 (1.15-1.57) for extrahepatic diseases, 1.50 (1.10-2.03) for circulatory diseases, 2.77 (1.49-5.15) for nephritis, nephrotic syndrome, and nephrosis, 4.08 (1.38-12.08) for esophageal cancer, 8.22 (1.36-49.66) for thyroid cancer, and 4.19 (1.18-14.94) for prostate cancer. Thus, the presence of HCV seropositivity increases the risk of death from a wide array of extrahepatic disease processes. Moreover, anti-HCV seropositives with detectable HCV RNA levels have a significantly greater mortality risk for death due to both hepatic and extrahepatic diseases processes than do individuals who are anti-HCV seropositives but who are HCV RNA negative. These data imply that individuals with chronic hepatitis C having an active infection manifested by HCV-RNA positivity should benefit from antiviral treatment to reduce both their overall mortality as well as hepatic disease mortality risk<sup>[10]</sup>.

Recently, the Center for Disease Control (CDC) has identified individuals born between 1945 and 1965 as well as veterans, males, people in low income groups, prisoners, those in various institutions, and African American as well as the Latino populations as being at higher risk for a HCV infection<sup>[11]</sup>. As the majority of infected individuals have little or no symptoms, they may never know that they are infected despite the

**Table 1** Individuals at high risk for hepatitis C virus infection

Individuals working in emergency departments
Anesthesiologists
First responders
Fire
Police
Ambulance attendants
Individuals undergoing chronic hemodialysis
Healthcare workers including employees in dialysis center
Institutional residents (prisons, individuals with physical, mental, and developmental abnormalities)
Individuals born between 1945-1965
Those receiving blood or blood products before 1992
Intravenous drug abusers
Presence of human immunodeficiency virus infection or individuals with high risk sexual behaviors

fact that 75%-80% of them may develop a lifelong chronic infection that adversely affects their life quality as well as their longevity. Individuals in this latter group also include those who received plasma or blood transfusions prior to 1992, hemophiliacs, individuals on hemodialysis, organ transplant recipients, those who experience needle sticks as a result of illicit drug use or an occupational exposures and possibly those infected as a result of tattoos or the use of unsterile equipment for body piercing, children born of a hepatitis C positive mothers and those who practice unprotected or high risk sex with multiple partners (Table 1). Most importantly, these asymptomatic individuals can unknowingly transmit the disease to others, thereby perpetuating the disease process in society at large<sup>[11,12]</sup>.

## THERAPY AND ERADICATION OF HCV

Historically, the available therapeutic agents utilized for the treatment of chronic hepatitis C (interferon-based therapies) have had only limited success at the elimination of the disease with efficacy rates ranging between 20% and 40% manifested as a sustained viral response (SVR) 6 mo after a presumed end of treatment (EOT) course of therapy<sup>[12]</sup>. In addition, these historical treatment regimens were expensive in terms of their direct and indirect costs, albeit less so than the new direct acting antiviral agents and had numerous adverse effect that limited their acceptability by individuals, who would have been considered as appropriate candidates for therapy. Moreover, the use of IFN-based therapies are contraindicated in individuals with a variety of autoimmune disease processes, those with a clinically significant depressive disorders, and those with advanced coronary artery or cerebrovascular disease. In addition, IFN-therapies have limited efficacy in individuals with different viral genotypes as well as specific genetic as well as phenotypic characteristics that include variant IL28B polymorphisms, obesity, diabetes mellitus, ethnicity

**Table 2** Goals of treatment of hepatitis C virus

Current goals of HCV treatment
Cure HCV infection in those infected with the virus
Reduce the downstream consequences of chronic hepatitis C
Prevent cirrhosis
Prevent decompensation of cirrhosis
Prevent hepatocellular carcinoma
Reduce the requirement for liver transplantation in individuals with chronic hepatitis C
Improve life quality of those with HCV
Reduction of all-cause as well as liver disease mortality
Ideal goals of HCV treatment:
Eliminate HCV disease in its all of varied manifestations (both hepatic and extrahepatic)
Reduce the number of individuals infected with minimal or no liver disease who are important transmitters of the virus within the population
Improve the life expectancy and quality of those infected with HCV regardless of the specific clinical presentation of their infection

HCV: Hepatitis C virus.

and coinfection with either HBV or HIV<sup>[13,14]</sup>.

In contrast, the newly developed direct acting (DAA) antiviral therapies are administered orally and require less complex regimes. As a result, they are more readily acceptable. As a consequence of their enhanced acceptability and increased rate of drug compliance, they achieve a significantly greater efficacy rate, have fewer adverse effects and appear not to be limited by the presence of a variety of concurrent medical disease processes to include the aforementioned genetic and phenotypic characteristics that adversely affect the outcome of interferon-based therapies. It is expected that the newer 3<sup>rd</sup> generation DAAs soon to be approved by the Food and Drug Administration (FDA) are even more efficacious and are effective across all genotypes as compared to the current 2<sup>nd</sup> generation DAA agents (Table 2)<sup>[15,16]</sup>.

By increasing the sustained virological response (SVR) to 90% or more from 2016 onward the number of treated cases in Belgium has been estimated to increase from 710 to 2050 in 2030 resulting in a reduction of the number of cases with cirrhosis, decompensated cirrhosis and HCC disease process which have high direct and indirect costs of care<sup>[17]</sup>. The new DAAs are reported to be most efficacious as compared to historical regimens with interferon when applied to F2-F4 cases. To obtain comparable outcomes with all cases ranging from those with F0-F4 fibrosis, 50% more cases would have to be treated, a number which would appear to be achievable with the greater acceptability and reduced frequency of adverse events associated with the newer agents. Additionally, a two-year delay in access to the DAAs has been estimated to increase HCV related morbidity and mortality by 15%. These data suggest that early rather than later therapy of HCV infected individuals would be even more efficacious than waiting particularly if it

**Table 3** Factors potentially contributing to fibrosis progression in individuals with chronic hepatitis C virus

Established factors <sup>1</sup>	More recently identified risk factors
Duration of HCV infection	Patient age at time of diagnosis
Older age at infection	Genotype 3 infection
Male gender	Insulin resistance
Presence of baseline fibrosis	Gene polymorphisms involved in inflammation and iron metabolism
HIV coinfection <sup>1</sup> /CD4 count < 200 cells/mL	Human leukocyte antigen DRB1*1201-3 allele
Long term alcohol consumption (> 20-50 g/d)	Latin ethnicity
HBV coinfection	Daily cannabis use
Metabolic syndrome (steatosis, insulin resistance, type 2 diabetes)	

<sup>1</sup>HCV viral load and mode of infection are not associated with faster fibrosis progression. HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; HBV: Hepatitis B virus.

includes all cases from F0-F4 hepatic disease<sup>[17]</sup>.

van der Meer *et al.*<sup>[18]</sup> have shown in an international, multicenter, long-term follow-up study from 5 large tertiary care hospitals in Canada and Europe consisting of 530 patients with chronic HCV infection, who started an interferon-based treatment regimen between 1990 and 2003, that the 10-year cumulative incidence rate of liver-related mortality or transplantation was 1.9% (95%CI: 0.0%-4.1%) with a prior SVR following treatment and 27.4% (95%CI: 22.0%-32.8%) without a SVR ( $P < 001$ ). Thus, in patients with chronic HCV infection and advanced hepatic fibrosis, a sustained virological response to interferon-based treatment is associated with a lower all-cause mortality rate and obviously a substantial reduction in overall direct and indirect costs of healthcare.

Molnar *et al.*<sup>[19]</sup> reported an association between HCV infection and the progression of chronic kidney disease. HCV infection was associated with a 2.2 fold increase in mortality, a 98% higher hazard of development of end-stage kidney, and a 15% worsening of renal function in a large cohort of United States veterans. In addition to death related to hepatocellular cancer, all-cause mortality increased with HCV infection was attributed in part to association with extrahepatic manifestations of HCV such as cryoglobulinemia, lymphoma, glomerulonephritides, as well as rheumatologic, hematologic, and dermatologic disorders.

Simmons *et al.*<sup>[20]</sup> reported in a meta-analysis and systematic review of 31 studies that achieving SVR in individuals with chronic HCV. After adjustment for potential confounding factors, the results of the pooled HR analysis revealed a decreased risk of all-cause mortality by approximately 50%, 74%, and 79% in the general populations, cirrhotic patients, and coinfecting (HCV/HIV) individuals respectively.

Sievert *et al.*<sup>[21]</sup> described three different treatment scenarios based upon the anticipated introduction of DAA regimens have been estimated to reduce the

overall HCV disease burden. Scenario 1 evaluated the impact of increased treatment efficacy alone estimated to be 80%-90% by 2016. Scenario 2 evaluated the increased expected efficacy as well as the increase in numbers of individuals expected to be treated from a value of 2550 to 13500 by 2018 without any treatment restrictions. Scenario 3 considered the same increases in efficiency and number expected to be treated limited to those with fibrotic disease  $\geq$  F3 during the period of 2015-2017. The authors estimated that 233490 people with chronic HCV infection. This group has included 13850 individuals with cirrhosis, 590 with HCC and 530 with liver-related deaths. Scenario 1 would result in a modest reduction in disease burden (4% decreases in HCC, decompensated cirrhosis, and liver deaths) and the overall costs related to these diseases. Scenario 3 had the greatest impact on disease burden projected at a 50% decrease in HCC, decompensated cirrhosis, and liver deaths and overall healthcare costs. Scenario 2 had only a slightly lower impact than did Scenario 3.

These data suggest that treatment regimens without any restrictions would result in a substantial reduction in health care costs and simultaneously reduce the number of infected individuals infected who can infect others (Table 3)<sup>[22,23]</sup>.

The development of the second-generation protease inhibitors (PIs) had a higher antiviral efficiency as a result of their plurigenotypic range but also as they were more convenient to administer and were associated with fewer side effects<sup>[24]</sup>. The NS5B inhibitors include nucleoside/nucleotide inhibitors (NIs) and non-nucleotide inhibitors (NNIs). NIs have even higher efficacy rates and even more useful as they can be used across all genotypes. Sofosbuvir has highly potent antiviral activity across all genotypes when used in association with pegylated interferon and ribavirin (PR). NS5A inhibitors (NS5A) also have potent antiviral activity and when used in combination with protease inhibitors are reported to achieve a SVR in GT-1b prior null responders to a prior interferon-based regimen. Several additional studies have demonstrated that interferon (IFN)-free regimens with DAA agent combinations achieve even higher rates of SVR in naïve as well as treatment-experienced GT-1 patients, who have failed prior interferon based treatment regimes. Moreover, quadruple regimens with peginterferon plus ribavirin (PR) achieve a SVR in almost all GT-1 null responders. The development of pan-genotypic direct-acting antiviral agents (NIs or NS5A.I) will allow additional new combinations with or without PR that are expected to increase the rate of SVRs for all patient populations regardless of genotype and those with cirrhosis<sup>[24]</sup>.

## COST OF HCV TREATMENT AND THE NEED FOR TIMELY THERAPY

In contrast to the recommendation for screening for

**Table 4** Extrahepatic manifestations associated with hepatitis C virus infection

Neuropsychiatric	Ocular
Depression	Corneal ulcer
Cerebral vasculitis	Uveitis
Endocrine	Autoimmune phenomena
hypothyroidism	CREST syndrome
Diabetes mellitus	Thyroiditis/hypothyroidism
Thyroiditis	Sicca syndrome
Neuromuscular	Renal
Weakness/myalgia	Membranous glomerulonephritis
Peripheral neuropathy	Nephrotic syndrome
Arthritis/arthralgia	Cryoglobulinemia related glomerulonephritis
Vascular	Hematologic
Necrotizing vasculitis	Aplastic anemia
Polyarteritis nodosa	Thrombocytopenia
Cryoglobulinemia	Non-Hodgkin's B cell lymphoma
Dermatologic	
Porphyria cutanea tarda	
Lichen planus	
Cutaneous necrotizing vasculitis	
Livedo reticularis	

HCV and the subsequent recognition of cases, the use of DAA therapy has been severely rationed by insurers as well as state and federal agencies. The cost of these drugs can be effectively reduced by an increase of the use of these agents to include all those patients infected with HCV rather than just those with advanced hepatic fibrosis<sup>[25,26]</sup>. The rationale for such rationing is that many of those recognized as having the disease will progress slowly over many years, many identified cases will not develop advanced liver disease manifested as advanced chronic hepatitis and cirrhosis (F3-4 cases) and experience any of the multiple complications of their liver disease requiring specific treatment<sup>[27-31]</sup>.

This reasoning fails to recognize the non-hepatic consequences of hepatitis C infection and the adverse effects of these non-hepatic diseases on patient's quality of life. This represents a short sided view of the cost of treatment of hepatitis C related disease (infections) and ignores the long-term costs of hepatitis C treatment consisting of the cost of treatment of cirrhosis, the cost of treatment of decompensated cirrhosis as well as the cost of treatment of HCC as well as the cost of liver transplantation and its long-term follow up. These costs far exceed the costs related to the treatment of hepatitis C before any of these complications occurs. In addition, this reasoning ignores the fact that hepatitis C infection is not limited to the liver *per se* and also includes a wide range of extra hepatic disease processes that occur in the absence of clinical liver disease and have extensive direct and indirect costs of their own (Table 4)<sup>[30-35]</sup>. These diseases affect adversely the individual's life quality and potentially longevity<sup>[36-41]</sup>. Most importantly, the exclusion of cases with recognized hepatic disease

ranging from those with F0 to F2 and those with extra hepatic disease processes fails to recognize that these individuals are the principal vectors for new cases of HCV infection<sup>[42-47]</sup>. Their treatment would be expected to greatly reduce the numbers of newly infected cases to include those with and without recognized hepatic disease and potentially eliminate the disease in the population at large<sup>[48-50]</sup>.

The rationing of therapy to those with advanced liver disease, also calls into question the ethical consequences of the recommendations of the CDC and other health related organizations and societies to screen individuals for the disease if no treatment is to be made available to those identified as having the disease. To do so under these circumstances only produces anguish and inappropriate fear in those identified as having the infection<sup>[51]</sup>.

The alternative approach of recognizing those that have the infection and treating them before they develop clinically evident disease associated with the tremendous costs to society in terms of direct and indirect costs of health care as a result of hepatic as well as the many extra hepatic disease processes known to occur as a result of hepatitis C infection should result in major long term reductions in health care costs<sup>[52]</sup>. Moreover, by treating these larger populations, the number of individuals, who unknowingly infect others and perpetuate the infection in the population, would be reduced with even greater overall health care cost reductions. The institution of this alternative approach incorporating a much larger population of infected individuals would make it possible for a marked reduction in cost per unit pill or course of therapy while maintaining the overall profit for pharmaceutical companies, who have expended large amounts of money to bring the drugs to market<sup>[52,53]</sup>.

Finally, at the day to day clinical level, treatment of patients with stages F0-F3 would be expected to be even more efficacious, be better tolerated with fewer cases dropping out of therapy than what would occur by delaying, treatment until more advanced stages of liver disease (cirrhosis, hepatic cancer, liver transplant) or not providing treatment at all<sup>[54]</sup>.

Younossi *et al.*<sup>[55]</sup> administered a questionnaire to 1923 individuals with chronic hepatitis C, genotype-1, who were enrolled in the ION trials and received HCV treatment of combination of ledipasvir and sofosbuvir (LDV/Sof) with a SVR-12 rate of 93.21%. Reduced work productivity secondary to absententeeism and presenteesim impairments dropped after achieving SVR-12 which would result in a productivity loss saving of 2.7 billion over one-year.

Tandon *et al.*<sup>[56]</sup> using a health insurance claims database from January 2001 to March 2012, compared a total of 1017 patients, who completed interferon therapy and 953 patients, who discontinued

therapy. Both resource utilization and healthcare cost statistically significant lower cost allocation of 3687 and 1644 dollars for all-causes and CHC-related healthcare costs, respectively, relative to those who discontinued therapy.

## CONCLUSION

Many patients achieve a SVR with PEG-IFN containing therapies. The continued improvements in the ability to obtain a SVR (expected cure) of HCV have been made within the past several years. The principal reason to utilize DAAs is to avoid the side effects of IFN which enhances acceptability, compliance and efficacy of treatment. The enhanced efficacy of these agents and the shorter duration of therapy are additional benefits.

Secondly, considerable increases in the burden of HCV-related advanced liver disease and its complications are expected to be seen in the United States utilizing current treatment regimens. The introduction of improved DAA regimens with enhanced efficacy and a non-restricted requirement for treatment should result in an even greater impact on the total health care costs and reduce the life-long costs of HCV disease management costs. A combination of increased treatment efficacy and greater utilization by treating all presentations of all the disease to include not only those with evident hepatic disease but also those without evidence of liver disease should result in major reductions in the lifetime costs of HCV related disease costs.

Finally, treating all HCV infected patients to include those with and without hepatic disease with DAA regimens will reduce the number of individuals developing advanced liver disease, reduce the cost of treating these cases and more importantly, reduce the cost of treatment of those with any form of HCV related disease to include not only those with F0-F2 fibrosis of the liver but also those with extra hepatic disease related to HCV infection with or without evidence for coexistent liver disease. Specifically, IFN-free regimens without liver staging requirements and including those without evidence of hepatic diseases but having recognized extrahepatic manifestations of HCV infection is projected to be the most cost-effective approach for treating HCV in all of its varied presentations. Therefore, treatment regimens without any restrictions would result in a substantial reduction in health care expenditure and simultaneously reduce the number of infected individuals who are infected can infect others.

## REFERENCES

- 1 **Boccaccio V**, Bruno S. Management of HCV patients with cirrhosis with direct acting antivirals. *Liver Int* 2014; **34** Suppl 1: 38-45 [PMID: 24373077 DOI: 10.1111/liv.12391]
- 2 **Bourlière M**, Wendt A, Fontaine H, Hézode C, Pol S, Bronowicki JP. How to optimize HCV therapy in genotype 1 patients with

- cirrhosis. *Liver Int* 2013; **33** Suppl 1: 46-55 [PMID: 23286846 DOI: 10.1111/liv.12067]
- 3 **Shiffman ML**, Benhamou Y. Patients with HCV and F1 and F2 fibrosis stage: treat now or wait? *Liver Int* 2013; **33** Suppl 1: 105-110 [PMID: 23286853 DOI: 10.1111/liv.12066]
- 4 **Afdhal NH**, Zeuzem S, Schooley RT, Thomas DL, Ward JW, Litwin AH, Razavi H, Castera L, Poynard T, Muir A, Mehta SH, Dee L, Graham C, Church DR, Talal AH, Sulkowski MS, Jacobson IM. The new paradigm of hepatitis C therapy: integration of oral therapies into best practices. *J Viral Hepat* 2013; **20**: 745-760 [PMID: 24168254 DOI: 10.1111/jvh.12173]
- 5 **Oramasionwu CU**, Moore HN, Toliver JC. Barriers to hepatitis C antiviral therapy in HIV/HCV co-infected patients in the United States: a review. *AIDS Patient Care STDS* 2014; **28**: 228-239 [PMID: 24738846 DOI: 10.1089/apc.2014.0033]
- 6 **Flores A**, Marrero JA. Emerging trends in hepatocellular carcinoma: focus on diagnosis and therapeutics. *Clin Med Insights Oncol* 2014; **8**: 71-76 [PMID: 24899827 DOI: 10.4137/CMO.S9926]
- 7 **Shiffman ML**. Hepatitis C virus therapy in the direct acting antiviral era. *Curr Opin Gastroenterol* 2014; **30**: 217-222 [PMID: 24625897 DOI: 10.1097/MOG.000000000000062]
- 8 **Sebastiani G**, Gkouvatso 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]
- 9 **Maan R**, van der Meer AJ, Hansen BE, Feld JJ, Wedemeyer H, Dufour JF, Zangneh HF, Lammert F, Manns MP, Zeuzem S, Janssen HL, de Knegt RJ, Veldt BJ. Effect of thrombocytopenia on treatment tolerability and outcome in patients with chronic HCV infection and advanced hepatic fibrosis. *J Hepatol* 2014; **61**: 482-491 [PMID: 24780302 DOI: 10.1016/j.jhep.2014.04.021]
- 10 **Lee MH**, Yang HI, Lu SN, Jen CL, You SL, Wang LY, Wang CH, Chen WJ, Chen CJ. Chronic hepatitis C virus infection increases mortality from hepatic and extrahepatic diseases: a community-based long-term prospective study. *J Infect Dis* 2012; **206**: 469-477 [PMID: 22811301 DOI: 10.1002/ijc.28753]
- 11 **Ward JW**. The epidemiology of chronic hepatitis C and one-time hepatitis C virus testing of persons born during 1945 to 1965 in the United States. *Clin Liver Dis* 2013; **17**: 1-11 [PMID: 23177279 DOI: 10.1016/j.cld.2012.09.011]
- 12 **Muir AJ**. The rapid evolution of treatment strategies for hepatitis C. *Am J Gastroenterol* 2014; **109**: 628-635; quiz 636 [PMID: 24732866 DOI: 10.1038/ajg.2014.66]
- 13 **Kohli A**, Shaffer A, Sherman A, Kottlil S. Treatment of hepatitis C: a systematic review. *JAMA* 2014; **312**: 631-640 [PMID: 25117132 DOI: 10.1001/jama.2014.7085]
- 14 **Feeney ER**, Chung RT. Antiviral treatment of hepatitis C. *BMJ* 2014; **348**: g3308 [PMID: 25002352 DOI: 10.1136/bmj.g3308]
- 15 **Pawlotsky JM**. New hepatitis C therapies: the toolbox, strategies, and challenges. *Gastroenterology* 2014; **146**: 1176-1192 [PMID: 24631495 DOI: 10.1053/j.gastro.2014.03.003]
- 16 **Kabiri M**, Jazwinski AB, Roberts MS, Schaefer AJ, Chhatwal J. The changing burden of hepatitis C virus infection in the United States: model-based predictions. *Ann Intern Med* 2014; **161**: 170-180 [PMID: 25089861 DOI: 10.7326/M14-0095]
- 17 **Stärkel P**, Vandijck D, Laleman W, Van Damme P, Moreno C, Blach S, Razavi H, Van Vlierberghe H. The Disease Burden of Hepatitis C in Belgium: An update of a realistic disease control strategy. *Acta Gastroenterol Belg* 2015; **78**: 228-232 [PMID: 26151693]
- 18 **van der Meer AJ**, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, Duarte-Rojo A, Heathcote EJ, Manns MP, Kuske L, Zeuzem S, Hofmann WP, de Knegt RJ, Hansen BE, Janssen HL. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA* 2012; **308**: 2584-2593 [PMID: 23268517 DOI: 10.1001/jama.2012.144878]
- 19 **Molnar MZ**, Alhourani HM, Wall BM, Lu JL, Streja E, Kalantar-Zadeh K, Kovesdy CP. Association of hepatitis C viral infection with incidence and progression of chronic kidney disease in a large cohort of US veterans. *Hepatology* 2015; **61**: 1495-1502 [PMID: 25529816]

- DOI: 10.1002/hep.27664]
- 20 **Simmons B**, Saleem J, Heath K, Cooke GS, Hill A. Long-Term Treatment Outcomes of Patients Infected With Hepatitis C Virus: A Systematic Review and Meta-analysis of the Survival Benefit of Achieving a Sustained Virological Response. *Clin Infect Dis* 2015; **61**: 730-740 [PMID: 25987643 DOI: 10.1093/cid/civ396]
  - 21 **Sievert W**, Razavi H, Estes C, Thompson AJ, Zekry A, Roberts SK, Dore GJ. Enhanced antiviral treatment efficacy and uptake in preventing the rising burden of hepatitis C-related liver disease and costs in Australia. *J Gastroenterol Hepatol* 2014; **29** Suppl 1: 1-9 [PMID: 25055928 DOI: 10.1111/jgh.12677]
  - 22 **Massard J**, Ratziu V, Thabut D, Moussalli J, Lebray P, Benhamou Y, Poynard T. Natural history and predictors of disease severity in chronic hepatitis C. *J Hepatol* 2006; **44**: S19-S24 [PMID: 16356583]
  - 23 **Poynard T**, Ratziu V, Charlotte F, Goodman Z, McHutchison J, Albrecht J. Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis c. *J Hepatol* 2001; **34**: 730-739 [PMID: 11434620]
  - 24 **Wendt A**, Adhoute X, Castellani P, Oules V, Ansaldi C, Benali S, Bourlière M. Chronic hepatitis C: future treatment. *Clin Pharmacol* 2014; **6**: 1-17 [PMID: 24470777 DOI: 10.2147/CPAA.S30338]
  - 25 **Hagan LM**, Sulkowski MS, Schinazi RF. Cost analysis of sofosbuvir/ribavirin versus sofosbuvir/simeprevir for genotype 1 hepatitis C virus in interferon-ineligible/intolerant individuals. *Hepatology* 2014; **60**: 37-45 [PMID: 24677184 DOI: 10.1002/hep.27151]
  - 26 **Myers RP**, Krajden M, Bilodeau M, Kaita K, Marotta P, Peltekian K, Ramji A, Estes C, Razavi H, Sherman M. Burden of disease and cost of chronic hepatitis C infection in Canada. *Can J Gastroenterol Hepatol* 2014; **28**: 243-250 [PMID: 24839620]
  - 27 **Vandijck D**, Moreno C, Stärkel P, Van Damme P, Van Vlierberghe H, Hindman SJ, Razavi H, Laleman W. Current and future health and economic impact of hepatitis C in Belgium. *Acta Gastroenterol Belg* 2014; **77**: 285-290 [PMID: 25090835]
  - 28 **Razavi H**, Elkhoury AC, Elbasha E, Estes C, Pasini K, Poynard T, Kumar R. Chronic hepatitis C virus (HCV) disease burden and cost in the United States. *Hepatology* 2013; **57**: 2164-2170 [PMID: 23280550 DOI: 10.1002/hep.26218]
  - 29 **Chan K**, Lai MN, Groessl EJ, Hanchate AD, Wong JB, Clark JA, Asch SM, Gifford AL, Ho SB. Cost effectiveness of direct-acting antiviral therapy for treatment-naïve patients with chronic HCV genotype 1 infection in the veterans health administration. *Clin Gastroenterol Hepatol* 2013; **11**: 1503-1510 [PMID: 23707354 DOI: 10.1016/j.cgh.2013.05.014]
  - 30 **Backx M**, Lewszuk A, White JR, Cole J, Sreedharan A, van Sanden S, Diels J, Lawson A, Neal KR, Wiselka MJ, Ito T, Irving WL. The cost of treatment failure: resource use and costs incurred by hepatitis C virus genotype 1-infected patients who do or do not achieve sustained virological response to therapy. *J Viral Hepat* 2014; **21**: 208-215 [PMID: 24438682 DOI: 10.1111/jvh.12132]
  - 31 **Hagan LM**, Yang Z, Ehteshami M, Schinazi RF. All-oral, interferon-free treatment for chronic hepatitis C: cost-effectiveness analyses. *J Viral Hepat* 2013; **20**: 847-857 [PMID: 24304454 DOI: 10.1111/jvh.12111]
  - 32 **Jacobson IM**, Cacoub P, Dal Maso L, Harrison SA, Younossi ZM. Manifestations of chronic hepatitis C virus infection beyond the liver. *Clin Gastroenterol Hepatol* 2010; **8**: 1017-1029 [PMID: 20870037 DOI: 10.1016/j.cgh.2010.08.026]
  - 33 **Hajarizadeh B**, Grebely J, Dore GJ. Epidemiology and natural history of HCV infection. *Nat Rev Gastroenterol Hepatol* 2013; **10**: 553-562 [PMID: 23817321 DOI: 10.1038/nrgastro.2013.107]
  - 34 **Chou R**, Hartung D, Rahman B, Wasson N, Cottrell EB, Fu R. Comparative effectiveness of antiviral treatment for hepatitis C virus infection in adults: a systematic review. *Ann Intern Med* 2013; **158**: 114-123 [PMID: 23437439]
  - 35 **Wei L**, Lok AS. Impact of new hepatitis C treatments in different regions of the world. *Gastroenterology* 2014; **146**: 1145-1150.e1-4 [PMID: 24662488 DOI: 10.1053/j.gastro.2014.03.008]
  - 36 **Carreño V**, Bartolomé J, Castillo I, Quiroga JA. New perspectives in occult hepatitis C virus infection. *World J Gastroenterol* 2012; **18**: 2887-2894 [PMID: 22736911 DOI: 10.3748/wjg.v18.i23.2887]
  - 37 **Castillo I**, Rodríguez-Iñigo E, Bartolomé J, de Lucas S, Ortíz-Movilla N, López-Alcorocho JM, Pardo M, Carreño V. Hepatitis C virus replicates in peripheral blood mononuclear cells of patients with occult hepatitis C virus infection. *Gut* 2005; **54**: 682-685 [PMID: 15831916]
  - 38 **Roque-Afonso AM**, Ducoulombier D, Di Liberto G, Kara R, Gigou M, Dussaix E, Samuel D, Féray C. Compartmentalization of hepatitis C virus genotypes between plasma and peripheral blood mononuclear cells. *J Virol* 2005; **79**: 6349-6357 [PMID: 15858018]
  - 39 **Roque-Cuellar MC**, Sánchez B, García-Lozano JR, Praena-Fernández JM, Márquez-Galán JL, Núñez-Roldán A, Aguilar-Reina J. Hepatitis C virus-specific cellular immune responses in sustained virological responders with viral persistence in peripheral blood mononuclear cells. *Liver Int* 2014; **34**: e80-e88 [PMID: 24127783 DOI: 10.1111/liv.12320]
  - 40 **Blackard JT**, Kemmer N, Sherman KE. Extrahepatic replication of HCV: insights into clinical manifestations and biological consequences. *Hepatology* 2006; **44**: 15-22 [PMID: 16799966]
  - 41 **Quiroga JA**, Llorente S, Castillo I, Rodríguez-Iñigo E, Pardo M, Carreño V. Cellular immune responses associated with occult hepatitis C virus infection of the liver. *J Virol* 2006; **80**: 10972-10979 [PMID: 17071928]
  - 42 **Carreño V**, Pardo M, López-Alcorocho JM, Rodríguez-Iñigo E, Bartolomé J, Castillo I. Detection of hepatitis C virus (HCV) RNA in the liver of healthy, anti-HCV antibody-positive, serum HCV RNA-negative patients with normal alanine aminotransferase levels. *J Infect Dis* 2006; **194**: 53-60 [PMID: 16741882]
  - 43 **Sagnelli E**, Sagnelli C, Pisaturo M, Coppola N. Hepatic flares in chronic hepatitis C: spontaneous exacerbation vs hepatotropic viruses superinfection. *World J Gastroenterol* 2014; **20**: 6707-6715 [PMID: 24944463 DOI: 10.3748/wjg.v20.i22.6707]
  - 44 **Richiardi L**, De Marco L, Gillio-Tos A, Merletti F, Fiano V, Palli D, Masala G, Agnoli C, Tagliabue G, Panico S, Mattiello A, Tumino R, Frasca G, Vineis P, Sacerdote C. Persistent infection by HCV and EBV in peripheral blood mononuclear cells and risk of non-Hodgkin's lymphoma. *Cancer Epidemiol* 2010; **34**: 709-712 [PMID: 20709616 DOI: 10.1016/j.canep.2010.07.014]
  - 45 **Tillmann HL**. Hepatitis C virus core antigen testing: role in diagnosis, disease monitoring and treatment. *World J Gastroenterol* 2014; **20**: 6701-6706 [PMID: 24944462 DOI: 10.3748/wjg.v20.i22.6701]
  - 46 **Choi YS**, Lee JE, Nam SJ, Park JT, Kim HS, Choi KH, Kim BS, Shin EC. Two distinct functional patterns of hepatitis C Virus (HCV)-specific T cell responses in seronegative, aviremic patients. *PLoS One* 2013; **8**: e62319 [PMID: 23638039 DOI: 10.1371/journal.pone.0062319]
  - 47 **Falcón V**, Acosta-Rivero N, Shibayama M. Evidences of hepatitis C virus replication in hepatocytes and peripheral blood mononuclear cells from patients negative for viral RNA in serum. *Am J Infect Dis* 2005; **1**: 34-42
  - 48 **Zignego AL**, Giannini C, Monti M, Gagnani L. Hepatitis C virus lymphotropism: lessons from a decade of studies. *Dig Liver Dis* 2007; **39** Suppl 1: S38-S45 [PMID: 17936221]
  - 49 **Natarajan V**, Kottilil S, Hazen A, Adelsberger J, Murphy AA, Polis MA, Kovacs JA. HCV in peripheral blood mononuclear cells are predominantly carried on the surface of cells in HIV/HCV co-infected individuals. *J Med Virol* 2010; **82**: 2032-2037 [PMID: 20981790 DOI: 10.1002/jmv.21906]
  - 50 **Angulo J**, Pino K, Pavez C, Biel F, Labbé P, Miquel JF, Soza A, López-Lastra M. Genetic variations in host IL28B links to the detection of peripheral blood mononuclear cells-associated hepatitis C virus RNA in chronically infected patients. *J Viral Hepat* 2013; **20**: 263-272 [PMID: 23490371 DOI: 10.1111/jvh.12076]
  - 51 **Slomski A**. WHO issues guidelines on HCV amid drug cost controversy. *JAMA* 2014; **311**: 2262-2263 [PMID: 24915242 DOI: 10.1001/jama.2014.5277]
  - 52 **van der Meer AJ**, Hansen BE, Fattovich G, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, Duarte-Rojo A, Manns MP, Ieluzzi D,

- Zeuzem S, Hofmann WP, de Knegt RJ, Veldt BJ, Janssen HL. Reliable prediction of clinical outcome in patients with chronic HCV infection and compensated advanced hepatic fibrosis: a validated model using objective and readily available clinical parameters. *Gut* 2015; **64**: 322-331 [PMID: 24815676 DOI: 10.1136/gutjnl-2013-305357]
- 53 **van der Meer AJ**, Veldt BJ, Feld JJ, Wedemeyer H, Dufour JF, Lammert F, Duarte-Rojo A, Manns MP, Zeuzem S, Hofmann WP, de Knegt RJ, Hansen BE, Janssen HL. The number needed to treat to prevent mortality and cirrhosis-related complications among patients with cirrhosis and HCV genotype 1 infection. *J Viral Hepat* 2014; **21**: 568-577 [PMID: 24118177 DOI: 10.1111/jvh.12185]
- 54 **Shiffman ML**, Benhamou Y. HCV F1/F2 patients: treat now or continue to wait. *Liver Int* 2014; **34** Suppl 1: 79-84 [PMID: 24373082 DOI: 10.1111/liv.12408]
- 55 **Younossi ZM**, Jiang Y, Smith NJ, Stepanova M, Beckerman R. Ledipasvir/sofosbuvir regimens for chronic hepatitis C infection: Insights from a work productivity economic model from the United States. *Hepatology* 2015; **61**: 1471-1478 [PMID: 25706754 DOI: 10.1002/hep.27757]
- 56 **Tandon N**, Balart LA, Laliberté F, Pilon D, Lefebvre P, Germain G, Prabhakar A. Impact of completing chronic hepatitis C (CHC) treatment on post-therapy healthcare cost. *J Med Econ* 2014; **17**: 862-871 [PMID: 25215925 DOI: 10.3111/13696998.2014.964720]

**P- Reviewer:** Enomoto H, Kaya M, Waisberg J **S- Editor:** Qiu S  
**L- Editor:** A **E- Editor:** Wang CH







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](mailto:bpgoffice@wjgnet.com)

Help Desk: <http://www.wjgnet.com/esps/helpdesk.aspx>

<http://www.wjgnet.com>

