BenEFiTs of Curing HepatiTis C InfecTion

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ABSTRACT

The hepatitis C virus (HCV) infection is one of the most important chronic viral infections worldwide and affects 3% of the world population, approximately 170-200 million people. The consequences of chronic infection are liver cirrhosis and hepatocellular carcinoma, which develop in 30-40% of the patients, leading to hepatic failure, need for liver transplantation and death. The hepatitis C virus is a RNA virus that is prevalent worldwide and is classified by the World Health Organization (International Agency for Research on Cancer) as one of the six oncogenic viruses. Hepatocellular carcinoma is one of the most important cancers and is fifth worldwide, but third in men in terms of mortality. Hepatitis C kills approximately 350,000 people every year, surpassing HIV infection in many countries as a cause of death.

Hepatitis C virus can kill in different ways: it can cause cirrhosis, cancer or severe liver disease in people co-infected with HIV. Hepatitis C treatment started in the mid 1980s with a 6% efficacy rate among patients taking thrice-weekly injections of human interferon. This therapy had numerous side effects. The efficacy of hepatitis C treatment has increased, and currently, the efficacy of the so-called direct antiviral agents (DAAs) is 80-90%. The benefits of a cure are enormous and include a lifetime negative serum HCV RNA, disappearance of HCV in the liver, regression of cirrhosis, decreased risk of developing hepatocellular carcinoma, disappearance of oesophageal varices, no more risk of HCV transmission to sexual partners or children, and increased survival.

At present, hepatitis C can be considered a curable disease.


INTRODUCTION

Chronic infection with the hepatitis C virus (HCV) affects approximately 170-200 million individuals worldwide, with an overall prevalence of 2.2-3.0% [1, 2]. The real incidence of HCV infection is uncertain because separating acute from chronic infection is difficult. However, from a global perspective, there will likely be an increase in incidence, mostly in developing countries [3]. In other regions, the incidence of hepatitis C has stabilised or even has decreased. However, in countries with high rates of immigration from endemic regions, the prevalence of HCV infection tends to increase. In Europe, an estimated 1.3% of the population carries HCV, with the highest rates in the southern and eastern regions and the lowest rates in the northern regions [4]. In North America [5], the prevalence of HCV appears to have stabilised or decreased, in contrast to what has occurred in Latin America [6] and the Far East [7].

Chronic HCV infection is a major cause of chronic liver disease, cirrhosis and liver cancer, particularly in the Western world and in some African countries, such as Egypt. Although hepatitis C is responsible for most cases of liver cancer and liver transplantation in developed countries, the available information on the burden of disease is largely incomplete or inconsistent [8]. This information is incomplete because the available studies do not fully capture the reality of infection, as many of them evaluate either a small sample of the population or groups at high risk for hepatitis C who were referred to tertiary centres. While these studies tend to exacerbate the burden of infection, those using the general population underestimate the true prevalence of the disease. The vast majority of individuals do not know they are infected due to the asymptomatic nature of the disease, advanced age and the low number of infected patients who receive antiviral therapy [9]. A significant increase in cirrhosis and HCV-related
Chronic hepatitis C infection is a slow progressive disease, appearing decades before patients develop complications, such as cirrhosis and HCC. Approximately 20% of patients are estimated to develop cirrhosis after 20-30 years of infection, although progression can be faster in elderly patients. Recent studies conducted in the U.S. indicate that this percentage could increase to 45% after patients live with the infection for 40-50 years [11]. Annually, 3 to 6% of patients with cirrhosis develop liver decompensation, and 1-4% develop HCC. HCV is an oncogenic virus, and chronic HCV infection is a common risk factor for HCC, particularly in the West and in Japan, where approximately 40-60% of patients with HCC have antibodies against HCV [12]. The rate of HCC has doubled or tripled in many countries in the last decade, and this increased incidence has been attributed to HCV infection. In addition, in some centres, HCC has become the most common complication and leading cause of death in patients with compensated cirrhosis associated with HCV [13, 14].

Chronic hepatitis C infection is the only global oncogenic chronic viral infection that can possibly be cured. Hepatitis B and HIV infect 350 and 34 million people worldwide, respectively, but there is no chance of a real cure in chronic cases.

Hepatitis C treatment began in 1985, with a 6% of virological response [15]. Step by step, in accordance with the evolution of molecular biology, genetics, immunology, pharmacology and clinical experience, the efficacy of hepatitis C therapy has increased. Currently, the efficacy is 80-90% with the latest medications, oral direct antiviral agents (DAAs) [16] (Fig. 1).

Several types of medications have been used to treat hepatitis C throughout these three decades. The first was human interferon (three times weekly), which had a less than 10% rate of success. In 1995, ribavirin was used in combination with interferon, and the sustained viral response (SVR) improved to 34-42%. In 2001, pegylated interferon (once weekly) was used in combination with ribavirin and had a 45% cure rate for genotype 1 and 70-80% for genotype 3 [17-19]. This double therapy paradigm has been the standard of care for a decade. In 2011, more progress was made with the combination of pegylated interferon and ribavirin with two protease inhibitors of the 3/4 region of the non-structural region of the virus, Boceprevir [20] and Telaprevir [21]. Triple therapy (pegylated interferon, ribavirin and DAAs) induces a sustained virological response rate of 70-80% in patients with genotype 1. In this context, outlining health policies to promote disease control and to reduce the rate of complications is imperative.

Several clinical trials are in rapid development worldwide for the new DAAs, which interact with several vital components of the virus (NS3/4, NS5, polymerase). In fact, a new generation of medications is rapidly approaching, including sofosbuvir, daclastavir, asunaprevir [22], ABT-450 [23], and faldaprevir [24]. Some of these medications are only oral agents that are used for a period of 12 weeks and have a few negligible side effects, leading to a chance of viral eradication in 80-90% of patients.

The efficacy of the therapy should be assessed using a sensitive test for serum HCV RNA. With the newer treatments, SVR can be achieved 12 weeks after finishing therapy instead of after 24 weeks. Patients with SVR are considered to be cured of the infection [25, 26]. More than 99% of patients who achieve SVR will never be positive again [27].

In fact, many advances have been made. The cure rate has increased from 6 to 90%, the treatment modality has changed from three injections a week to a few pills a day, and treatment duration has decreased from 48 weeks to only 12 weeks.

Hepatitis C: The Benefits of a Cure

Chronic hepatitis C infection is a physical, mental and social disease, affecting the individual, the couple, the family, and the society as a whole. Hepatitis C is an infection, a liver disease, a cancer, and a psychological and social stressor.

The benefits of cure are enormous (Table I). When SVR or virological cure occurs, the effect is lifelong and is actually viral eradication [28]. The virus is not detectable in liver cells [29, 30] as indicated by the presence of HCV RNA according to PCR in liver [31] or mononuclear blood cell samples [32, 33]. The genotype becomes and remains negative because there is no virus available for detection. The ALT, AST and GGT become normal for life [34, 35].

Anti-HCV (a marker of past infection) generally remains positive. The titre can decrease slowly, and anti-HCV can become negative several years later, as in the case of acute hepatitis C, which is the so-called seroreversion [36, 37].

On hepatic elastography (Fibroscan®), the liver stiffness values decrease over a few months [38]. In patients with advanced fibrosis at the start of therapy, liver stiffness is significantly reduced during treatment, but improvement continues after treatment only in patients who achieve a SVR. A liver stiffness assessment earlier than 6 months after the end of therapy does not appear to be clinically meaningful [39, 40].

Abdominal ultrasound findings can change. Previously irregular liver contours can become regular, and the diameter

Fig. 1. Advances in the therapy of chronic hepatitis C. IFN: interferon; RBV: ribavirin; PEG: PegInterferon; DAAs: Direct-acting antiviral agents.
of the portal vein or spleen volume [41, 42] can decrease in the presence of portal hypertension. Lymph nodes in the hepatic hilum can disappear [43, 44]. There are some studies showing that the dimensions of these lymph nodes are related to the level of viral replication [45].

There is an improvement in the quality of life[46, 47], asthenia, fatigue [48], general well-being [49] and psychological state (anxiety and/or depression) [50, 51].

The risk of sexual [52] and perinatal transmission disappear after cure [53]. These benefits are very important advantages of a SVR in treating hepatitis C. We can consider the cure as “belonging” not only to the patient but also to his or her family or partner. HCV infection is also a familial disease. Insurance companies must decrease the insurance premium because there is less risk of clinical evolution [54].

There are reports of the control and even disappearance of some associated conditions, such as porphyria cutanea tarda [55, 56], polyneuropathy [57] urticaria [58], cryoglobulinemia [59], splenic lymphoma [60, 61], B-lymphoma [62], glomerulonephritis [63], vasculitis leucocytoclastic [64], cerebral vasculitis not related to cryoglobulinemia [65, 66], and central and peripheral demyelination [67]; there are also beneficial effects on cerebral metabolism and selective aspects of neurocognitive function [68].

Depending on the country and burden of the infection, treating hepatitis C with double and triple therapy [69, 70] has been proven to be cost-effective [71, 72].

Reducing personal, psychological, family and social stigma is a huge benefit for everyone.

### HEPATITIS C THERAPY, CIRRHOSIS AND HEPATOCELLULAR CARCINOMA

Regarding liver disease, the risk of progression to cirrhosis decreases. In some cases, patients experience a reversal of cirrhosis [73]. In fact, cirrhosis is no longer an irreversible condition, as was thought some years ago; oesophageal varices can also disappear [74, 75]. There can also be an increase in platelets in patients with thrombocytopenia [76]. Moreover, there is a decreased risk of evolution into more severe stages of liver disease, such as HCC [77] and decompensated liver disease (ascites, jaundice, rupture of oesophageal varices, encephalopathy) [78]. Survival increases, and liver-related mortality is clearly reduced [79, 80].

In cases where liver transplantation is necessary, the risk of reactivation is no longer present. More than 95% of patients transplanted for HCV-associated cirrhosis become HCV RNA positive again. Around 50% develop severe forms of liver disease a few years after transplantation [81, 82].

Although the chance of developing HCC is significantly reduced in patients with cirrhosis [83, 84], the risk remains [85, 86], warranting an abdominal ultrasound every six months.

Cirrhosis is the major risk factor for developing HCC. Hepatitis C virus (HCV)-related cirrhosis is the leading cause of HCC in most Western countries. HCC is usually the first complication to develop and the main cause of death in patients with compensated cirrhosis. Hepatocellular carcinoma development and mortality have been found in several studies to be significantly lower in patients achieving HCV eradication compared to non-responders to IFN. Viral eradication has an important benefit in the natural history of HCV-related cirrhosis. Multivariate analysis has shown that non-SVR is a common predictor of all clinical outcomes, particularly HCC development. Despite a very low incidence, HCC can still occur in sustained responders many years after stopping IFN therapy. Some authors have shown that the incidence of HCC gradually increases over a

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**Table I. Benefits of curing hepatitis C infection**

<table>
<thead>
<tr>
<th>Biochemical, virological</th>
<th>Negative HCV RNA (viral load) for life in more than 99% of cases</th>
<th>Disappearance of HCV RNA in the liver</th>
<th>Disappearance of HCV RNA in peripheral blood mononuclear cells</th>
<th>No detection of the genotype</th>
<th>Possible seroreversion (negative detection) of anti-HCV</th>
<th>Normalisation of aminotransferases (AST, ALT) and GGT</th>
<th>Platelet increase in patients with thrombocytopenia</th>
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<tbody>
<tr>
<td><strong>Ultrasound, elastography</strong></td>
<td>Regular liver contours</td>
<td>Reduction in portal vein diameter in the case of portal hypertension</td>
<td>Disappearance of lymph nodes near the hepatic hilum</td>
<td>Normalisation of Elastography (Fibroscan®) values</td>
<td>Disappearance of splenomegaly</td>
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<tr>
<td><strong>Liver disease</strong></td>
<td>Reduced risk of progression to cirrhosis</td>
<td>Reversion of cirrhosis in some cases</td>
<td>Disappearance of oesophageal varices</td>
<td>Reduced risk of progression to liver cancer</td>
<td>Reduced risk of decompensated liver disease (ascites, jaundice, rupture of oesophageal varices, encephalopathy)</td>
<td>Disappearance of the risk of recurrence after liver transplantation</td>
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<td><strong>Transmission</strong></td>
<td>Disappearance of the risk of sexual transmission</td>
<td>Disappearance of the risk of perinatal transmission</td>
<td>No transmission to others (intravenous drug users). Benefit to public health</td>
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<td><strong>Well-being, quality of life</strong></td>
<td>Improved quality of life (disappearance of asthenia, fatigue, general well-being)</td>
<td>Reduced psychological impact (anxiety/depression)</td>
<td>Reduced personal, family and social stigma</td>
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<td><strong>Economic</strong></td>
<td>Cost-effectiveness of treatment</td>
<td>Decrease in health insurance premiums</td>
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<td><strong>Other</strong></td>
<td>Cure/improvement of associated conditions (porphyria cutanea tarda, polyneuropathy, urticaria, cryoglobulinemia, splenic lymphoma, glomerulonephritis, vasculitis leucocytoclastic, central nervous system vasculitis, demyelination, beneficial effect on cerebral metabolism and selective aspects of neurocognitive function)</td>
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<td><strong>Survival</strong></td>
<td>Reduced risk of death from liver disease in the setting of liver cirrhosis, liver cancer, co-infection with HIV and HCV and liver transplantation</td>
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period of at least 9 years after stopping treatment [87]. Several studies have shown that, in general, the diagnosis of HCC is made in the first 3 years after therapy [88]. What these studies emphasize is that identifying those patients who remain at risk of developing HCC after SVR and maintaining surveillance because HCC may occur several years after eradication are clinically relevant. The development of HCC in patients with cirrhosis is a multifactorial process that is influenced by male sex, alcohol use, diabetes, smoking, prior hepatitis B infection, and steatosis; however, the main risk factor is the presence of cirrhosis.

Hepatitis C treatment in patients with or without cirrhosis can be considered an anti-oncogenic therapy because the risk of evolution to liver cancer is greatly reduced.

CONCLUSION

From a global perspective, curing HCV chronic infection can be considered a real benefit to public health mainly by reducing the risk of complications and death from liver disease. With access to the most up-to-date therapies, the disease is almost curable, and the efficacy of treatment markedly increases the survival of infected patients. Chronic hepatitis C infection is a strongly stigmatised silent epidemic and a global chronic disease, but there is a strong chance for a definitive cure.

Conflicts of interest: Rui Marinho has been speaker/advisory board for Abbvie, Gilead, MSD, Roche, Brystol Myers-Squibb, Janssen; José Velosa has been speaker/advisory board for Gilead, MSD, Roche, Brystol Myers-Squibb, Janssen.

Authors contribution: Marinho RT, Vitor S, and Velosa J made substantial contributions to the conception and design of the study, acquisition of data, or analysis and interpretation of data; drafted the article or revised the manuscript critically for important intellectual content; and gave final approval of the version to be published.

REFERENCES


