Research, Society and Development, v. 9, n. 7, e688974645, 2020
(CC BY 4.0) | ISSN 2525-3409 | DOI: http://dx.doi.org/10.33448/rsd-v9i7.4645

Farias, JVC, Farias, ICC, Macedo, PR & Moura, PMMF (2020) Clinical and epidemiological overview of liver fibrosis and hepatocellular carcinoma in patients infected with the hepatitis C virus. ***Research, Society and Development,*** *9*(7):1-18, e688974645.

Panorama clínico e epidemiológico da fibrose hepática e carcinoma hepatocelular em pacientes infectados pelo vírus da hepatite C

Clinical and epidemiological overview of liver fibrosis and hepatocellular carcinoma in patients infected with the hepatitis C virus

Panorama clínico y epidemiológico de la fibrosis hepática y el carcinoma hepatocelular en pacientes infectados con el virus de la hepatitis C

Recebido: 18/05/2020 | Revisado: 23/05/2020 | Aceito: 25/05/2020 | Publicado: 04/06/2020

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Resumo

Cerca de 2,4 milhões de pessoas morrem por ano no mundo como consequência da infecção crônica pelo vírus da hepatite C (VHC). O VHC representa um problema de ordem mundial, mais de 170 milhões de pessoas estão infectadas pelo vírus em todo o mundo, correspondendo a cerca de 3% da população. Alguns sinais comuns à pacientes infectados cronicamente pelo VHC são: atividade de enzimas hepáticas aumentadas e doenças crônicas do fígado, tais como

fibrose, cirrose e carcinoma hepatocelular. O presente estudo é constituído por uma revisão bibliográfica, de natureza qualitativa e tem como objetivo abordar os principais aspectos clínicos e epidemiológicos da infecção crônica pelo VHC. A detecção do VHC é realizada através da pesquisa de anticorpos por ensaio de imunoabsorção enzimática (ELISA) e pesquisa do VHC-RNA através de reação em cadeia da polimerase (PCR). As técnicas de detecção atuais não são uma realidade para todos os centros médicos e ambulatórios, fazendo-se necessário o desenvolvimento de novas técnicas de detecção, uma vez que o aparato tecnológico para realização de pesquisa do VHC-RNA, bem como da ELISA são uma realidade distante para grande parte do sistema de saúde mundial. O desenvolvimento de antivirais de ação direta aumentou a resposta viral, alcançando até 92,7% de sucesso. Faz-se necessário o acompanhamento de pacientes pós-tratamento, bem como o tratamento de pacientes que ainda estão acometidos pelo vírus mundialmente, para garantir que não haja progressão de fibrose hepática em cirrose e nem, tampouco, o desenvolvimento de CHC. Adicionalmente, deve-se manter a vigilância, para possíveis mutações e surgimento de resistência viral aos DAAs.

Palavras-chave: Vírus da hepatite C; Fibrose hepática; Carcinoma hepatocelular; Antivirais de ação direta.

Abstract

About 2.4 million people die each year worldwide as a result of chronic infection with the hepatitis C virus (HCV). HCV is a worldwide problem, more than 170 million people are infected with the virus worldwide, corresponding to about 3% of the population. Some common signs for patients chronically infected with HCV are: increased liver enzyme activity and chronic liver diseases, such as fibrosis, cirrhosis, and hepatocellular carcinoma. The present study consists of a literature review, of a qualitative nature which aims to approach the main clinical and epidemiological aspects of the chronic infection caused by the HCV. HCV detection is carried out by screening for antibodies by enzyme-linked immunosorbent assay (ELISA) and screening for HCV-RNA through polymerase chain reaction (PCR). The current detection methods are not viable for all medical centers and outpatient clinics, making it necessary to develop new detection methods, since the technological apparatus for screening HCV-RNA, as well as ELISA, is a distant reality for the vast majority of the global health system. The development of direct-acting antivirals (DAAs) increased the viral response, reaching up to 92.7% success rate. It is necessary to monitor post-treatment patients, as well as to treat patients who are still affected by the virus worldwide, to ensure

that there is no progression of liver fibrosis in cirrhosis, nor the development of HCC. Additionally, vigilance should be maintained for possible mutations and the emergence of viral resistance to DAAs.

Keywords: Hepatitis C virus; Liver fibrosis; Hepatocellular carcinoma; Direct-acting antivirals.

Resumen

Alrededor de 2.4 millones de personas mueren cada año en todo el mundo como resultado de una infección crónica con el virus de la hepatitis C (VHC). El VHC es un problema mundial, más de 170 millones de personas están infectadas con el virus en todo el mundo, lo que corresponde a aproximadamente el 3% de la población. Algunos indicios comunes para pacientes con infección crónica por VHC son: aumento de la actividad enzimática del hígado y enfermedades hepáticas crónicas, como fibrosis, cirrosis y carcinoma hepatocelular. El presente estudio consiste en una revisión de la literatura, de naturaleza cualitativa tiene como objetivo abordar los principales aspectos clínicos y epidemiológicos de la infección crónica por el VHC. La detección del VHC se realiza mediante la detección de anticuerpos mediante un ensayo inmunoabsorbente ligado a enzimas (ELISA) y la detección de RNA del VHC a través de la reacción en cadena de la polimerasa (PCR). Las técnicas de detección actuales no son una realidad para todos los centros médicos y clínicas ambulatorias, por lo que es necesario desarrollar nuevas técnicas de detección, ya que el aparato tecnológico para realizar investigaciones sobre RNA-VHC, así como ELISA es una realidad distante para gran parte del sistema de salud global. El desarrollo de antivirales de acción directa aumentó la respuesta viral, alcanzando una tasa de éxito de hasta el 92.7%. Es necesario monitorear a los pacientes después del tratamiento, así como tratar a los pacientes que todavía están afectados por el virus en todo el mundo, para asegurar que no haya progresión de la fibrosis hepática en la cirrosis, ni el desarrollo de CHC. Además, se debe mantener la vigilancia de posibles mutaciones y la aparición de resistencia viral a los DAAs.

Palabras clave: Virus de la hepatitis C; Fibrosis hepática; Carcinoma hepatocelular; Antivirales de acción directa.

1. Introduction

Approximately 2.4 million people die each year worldwide as a result of chronic infection with the hepatitis C virus (HCV) (Ly et al., 2012). HCV is a worldwide problem,

notably more than 170 million people are infected with the virus worldwide, corresponding to about 3% of the world population. According to the World Health Organization (WHO), 3-4 million new chronic infections are observed annually (World health organization, 2010) and 1.9% of all infected people in the world are in Brazil (Shire & Sherman, 2015). In the Northeast, the prevalence of HCV-infected individuals is estimated at around 1% in adults aged 20-69 years, corresponding to more than 50 thousand people potentially infected in this region (Pereira et al., 2013).

Main pathway of HCV transmission is through direct contact with blood, contaminated syringes or non-disposable glass syringes and blood transfusions, which are some of the important factors that contributed to the cosmopolitan distribution of the virus (Colvin, 2010). In recent years, the main form of contamination has been the use of injectable drugs. Furthermore, men who have sex with other men have been considered a risk group for HCV transmission (Hajarizadeh, Grebely, & Dore, 2013). HCV infection is often asymptomatic and can remain undiagnosed for several years, often being discovered by chance (Rehermann & Bertoletti, 2015).

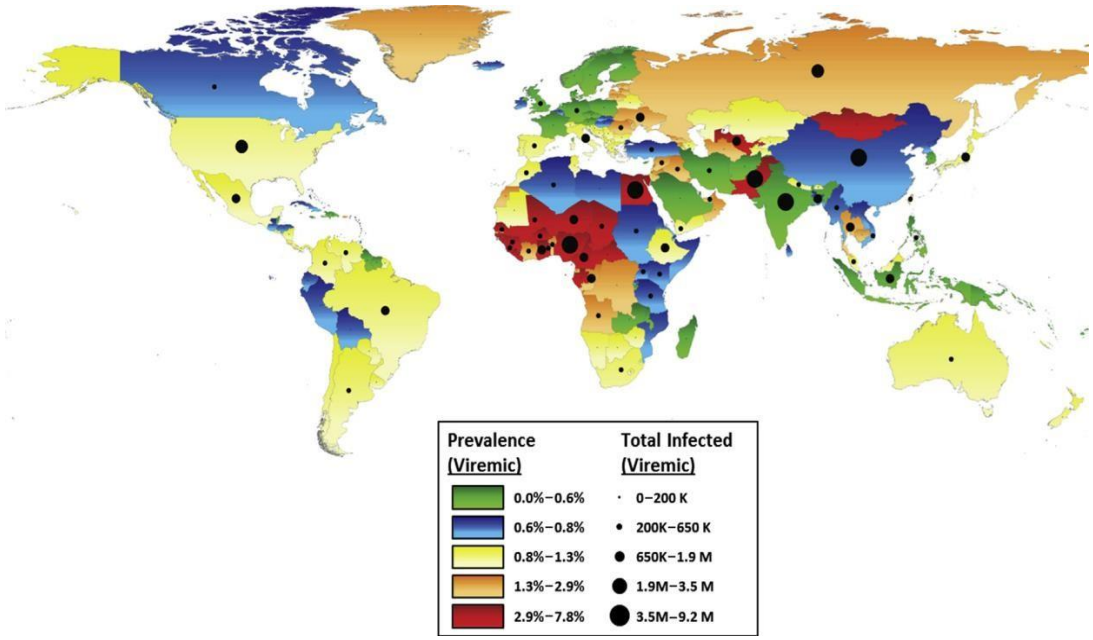
National Academies Institute of Medicine (IMNA) estimates that about 75% of all cases of HCV infected patients remain undiagnosed. The Center for Contagious Diseases estimates that people that were born between 1945-1969 of the American population, which corresponds to 27% of the entire population, represent 75% of all cases of chronic hepatitis in the country, and 73% of all cases of mortality caused by HCV, presenting a higher risk of developing more severe stages of hepatic fibrosis and hepatocellular carcinoma (HCC) (Colvin, 2010).

O objetivo do presente estudo é abordar os principais aspectos clínicos e epidemiológicos da infecção crônica pelo VHC.

2. Prevalence

HCV prevalence tends to vary according to the country's level of industrialization and development. The highest prevalence of HCV is in poor countries, such as some African countries, while wealthier nations, such as European and North American countries, tend to have a lower prevalence, as shown in Figure 1.

Figure 1: Overview of HCV infection worldwide.



Source: Shire & Sherman, 2015.

The image portraits in color the percentage of viremic concerning the total world population, and the size of the circumference indicates the total number of infected people in thousands within the country.

It is possible to discern the prevalence of viremic being strictly related to the country's levels of wealth. Thus, a higher prevalence is observed in sub-Saharan African countries, while lower prevalence is observed in Canada and wealthy European countries. The size of the circumference indicates the total number, regardless of the country's sizes. Hence, the low prevalence of viremic in China in relative numbers (percentage) combined with the considerably elevated absolute number of infected.

The HCV infection is a worldwide spread disease, which leads to several complications in the patients. For this reason, it is necessary to better understand the physiopathology of this disease and its complications. Therefore, the objective of this study is to approach the major clinical and epidemiological aspects of HCV chronic infection.

2. Methods and Materials

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The study is a bibliographic review, of a qualitative nature, with an exploratory characteristic as recommended by Pereira et al. (2018). Consisting of articles selected through

searches in national and international databases, such as National Library of Medicine (PUBMED), Medical Literature Analysis and Retrieval System Online (MEDLINE), Latin American and Caribbean Literature in Health Sciences (LILACS), Virtual Health Library (VHL) and Scientific Electronic Library Online (SciELO), in addition to the Google Scholar tool, as well as the Ministry of Health manuals, dissertations and free theses found in full format, from 2005 to 2020 and include the keywords used (Hepatitis C virus; liver fibrosis; hepatocellular carcinoma; direct-acting antivirals).

3. Viral Genotypes

HCV is a positive polarity RNA virus that belongs to the family Flaviviridae and genus Hepacivirus (Ferenci, Fried & Labrecque, 2010), which has an envelope in its external structure (Smith et al., 2014). The distribution of HCV genotypes varies according to the transmission pathways and ethnic variability. There is significant variability in the HCV genome within the primary structure of its RNA, it can be grouped into genotypes 1 to 7 and its consequent subtypes, such as 1a, 1b, 2a, 2b, etc., those are divided into multiple subtypes, such as 1a, 1b, 3a, 2a. The genotyping of the virus is carried out by sequencing the *E1* and *NS5B* genes (Smith et al., 2014).

Genotype 1 is the most common, totaling 83.4 million cases (46.2%) of all cases of chronic HCV infection worldwide. This genotype has a wide geographical distribution, being present in Western Europe, North and South America, Asia, and Australia (Hajarizadeh et al., 2013; Smith et al., 2014). HCV genotype 2 is present in the West and Central Africa (Karoney & Siika, 2013; Lavanchy, 2011). Genotype 3 is the second most common, representing a total of 54.3 million cases (30.1%) worldwide and occurs predominantly in South Asia (Messina et al., 2015). Genotype 4 occurs in the Middle East, more predominantly in Egypt (Karoney & Siika, 2013). Genotype 5 is present only in South Africa. Genotype 6 is endemic to Southeast Asia. Genotype 7 was reported in only one case, isolated in Canada, coming from an immigrant from Central Africa (Hajarizadeh et al., 2013; Lavanchy, 2011).

The cosmopolitan distribution characteristic of the virus is established by its high mutational capability, adapting to different ethnicities and genetic backgrounds, with the capability for infection and worldwide transmissibility.

4. Severe Advancements Linked with HCV Infection

Some common signs for patients chronically infected with HCV are elevated liver enzyme activity and chronic liver diseases, such as fibrosis, cirrhosis, and HCC (Friedman, 2010). It is estimated that 20% of these chronically infected patients will progress to liver cirrhosis and / or hepatocellular carcinoma (Rehermann & Bertoletti, 2015). Worldwide, HCV is responsible for 27% of cirrhosis cases and 25% of HCC cases it is estimated that 50% of all HCC cases are caused by HCV (World Health Organization, 2010). On the other hand, moderate or severe liver fibrosis occurs more in women (55%) (Carmo et al., 2016).

4.1 Fibrogenesis

Fibrosis is the most commonly used parameter for a correct assessment of the progression of hepatitis C chronic disease (D'Ambrosio et al., 2013). In hepatic fibrosis, apoptotic bodies accumulate with excessive deposition of proteins in the extracellular matrix, such as collagen, laminin, elastin, and fibronectin, followed by tissue healing and stiffening with loss of cellular and physiological function (Friedman, 2010). Viral infection modulates metabolic and signaling pathways through viral proteins. The virus indirectly induces the antiviral responses of the immune system, leading to a process of chronic infection. Innate immunity plays a key role in the etiology of liver fibrosis, involving subpopulations of lymphocytes, as well as dendritic cells and macrophages responding to the constant damage caused to the liver (Peng et al., 2012).

The increase in portal pressure associated with fibrosis modifies the architecture flow and a dynamic increase in pressure mediated by the contraction of myofibroblasts and hepatic stellate cells (HSCs), which are considered the main mediators of the fibrogenic process (Pellicoro et al., 2014). Infection with HCV mediated by DC-SIGN (dendritic cell-specific intercellular adhesion molecule-grabbing nonintegrin) triggers the activation of the fibrogenesis process. Multiple growth factors, proinflammatory cytokines, and chemokines can regulate the activation of HSCs in myofibroblasts (Pradere et al., 2013). An important pro-fibrotic agent is the platelet-derived growth factor (PDGF) and its subsequent effects of intracellular calcium mobilization on HSCs. Growth factor α derived from Kupffer cells (TGFα) also promotes the proliferation of HSCs. Additionally, the vessel endothelial growth factor (VEGF) contributes to the activation and proliferation of HSCs, as well as hepatic angiogenesis, making this molecule play a crucial role in the fibrogenic process (Svegliati-

Baroni et al., 2005). HCV-infected hepatocytes infiltrate the inflamed tissue, releasing several pro-fibrogenic factors. Among the main fibrogenic factors are the growth transformation factor B-1 (TGF-B1) which may increase the levels of tissue metalloproteinase inhibitor (TIMP-1), therefore blocking the action of the enzymes responsible for maintaining the extracellular matrix (MMP-1 and MMP-9). Metalloproteinases play an important role in physiological functioning, as in processes of cell proliferation, apoptosis, inflammation, aging, and cancer (Peng et al., 2012). MMPs have an important interstitial collagenase function, participating in the initial cleavage of the collagen helix, leaving it susceptible to degradation by other enzymes that are constantly produced in the liver tissue. The presence of a liver injury leads to the activation of HSCs, which is associated with an increase in TIMP-1. The increase in TGF-B1, therefore, would be associated with the activation of HSCs / myofibroblasts and increased expression of TIMP-1, in which matrix degradation favors the formation of a network in hepatic fibrosis. TIMP-1 is an important serum marker for collagen metabolism, as well as for the maintenance of the extracellular matrix (Friedman, 2008; Pellicoro et al., 2014). An increase in TGF-B1 levels would then increase the regulation of inflammation, possibly leaving the organs more susceptible to fibrosis.

The detection of fibrosis can be done through liver biopsy, an invasive procedure, or transient hepatic elastography (Fibroscan), non-invasive (D'Ambrosio et al., 2013). In a liver biopsy, a fragment of the liver is collected for macroscopic and microscopic analysis, determining the degrees of fibrosis and inflammation. The biopsy is classified by the METAVIR scale, where the degrees indicate respectively; F0- without fibrosis; F1- portal fibrosis without septa; F2- portal fibrosis with rare septa; F-: fibrosis with numerous septa, without cirrhosis and F4- cirrhosis (Friedman, 2010). On the other hand, fibroscan takes into account the speed of wave propagation in the liver parenchyma, which is measured in kPA (kilopascals), taking into account the elasticity of the liver, where the greater the stiffness, the greater the degree of fibrosis of the patient (D'Ambrosio et al., 2013). Indices and algorithms have been used to predict the degree of fibrosis without the need for biopsies, such as the APRI (aspartate aminotransferase to platelet ratio index). While FIB-4 (fibrosis-4) takes into consideration age, AST, ALT (alanine aminotransferase), and platelet count (Lin, Xin & Dong, 2011) as parameters. Patients in the earliest stages of fibrosis (F0 - F1) are not usually treated with DAAs (direct-acting antivirals), however, they should be monitored for risk of progression of liver fibrosis, so that it is possible to anticipate and start treatment in initial stages of disease progression (Aasld, 2015).

The form of viral replication in hepatocytes, as well as mediators of the immune

response, have supported the fact which liver fibrosis may be considered the main marker of the stage of the chronic disease caused by HCV, indicating a direct relation to the disease progression.

4.2 Hepatocellular carcinoma

The main cause of HCC development is the presence of chronic disease caused by the hepatitis B virus (HBV) or HCV, factoring about 70% of all HCC cases. About 70% of patients affected by HCC are male (Carmo et al., 2016). Hepatocellular carcinoma is the most common type of liver cancer, representing the fifth among all types of cancer and second in mortality rate, with incidence growing between 3-9% per year (El-Serag, 2011; Petrick et al., 2016) The early stage of HCC is asymptomatic, making early detection difficult (Bruix, Reig & Sherman 2016).

HCC has been classified by WHO (2010) into five different subtypes: fibrolamellar HCC, fibrous HCC, undifferentiated HCC, sarcomatoid HCC, and lymphoepithelioma-like HCC. The diagnosis and differentiation are made through cytohistological observations.(Bosman et al, 2010.). Recently, morphological analyzes and characterizations of new HCC subtypes have been carried out, including steatohepatic HCC (Torbenson, 2017). Steatohepatic HCC is induced by cirrhosis caused by chronic disease resulting from HCV infection. The main feature of steatohepatic HCC is the thickening of the blood vessel wall, ductular reaction, and dense fibrous septa. This subtype has characteristics similar to conventional HCC (Deniz, 2017).

Inflammation caused by the chronic form of HCV leads to a modulation of cytokines, which favors the formation of a tumor microenvironment (Kanda, Yokosuka, & Omata, 2013). Several serum miRs have been considered important factors for the deregulation of HCC caused by HCV, such as the upregulation of G1 cyclin, caused by miR 122 (Hsu et al., 2012), and miR 34, which has been associated with downregulation of HSP-70 (heat shock protein), both factors would increase the carcinogenic potential, since the deregulation of these proteins leads to a cycle of non-pre-cell divisions programmed, favoring the tumor microenvironment (Shehata et al., 2017).

Unlike fibrogenesis, carcinogenesis is not as well established and detailed when in association with HCV or simply by other processes, new studies continue to be carried out to increase clarification of this pathway. The lack of effective and established therapy makes it necessary to carry out subsequent studies that can analyze carcinogenesis after viral

eradication.

5. HCV Detection

HCV detection is carried out by screening for antibodies by enzyme-linked immunosorbent assay (ELISA), as well as screening for HCV-RNA through polymerase chain reaction (PCR) (Rafik et al., 2016).

ELISA is the most commonly used one, which screens for anti-HCV antibodies. The third-generation ELISA can be performed to detect the core viral antigens, NS3, NS4, and NS5 (Ali et al., 2015). Anti-HCV antibodies begin to be produced about 70 days after a viral infection, making this the gold standard for diagnosing chronic disease (Cresswell et al., 2015).

To perform ELISA, 2 ml of serum sample is collected from each patient, separated into two 1 ml aliquots each and placed in identified microtubes and stored at -20 °C until the analyzes are performed. Different kits may be used, including commercial kits, such as the KIT HK 326 commercial kit (Hycult biotechnology), following the manufacturer's instructions (Ghany et al., 2009).

The ELISA plates are sensitized in carbonate buffer and HCV antigen previously diluted to 1/200 containing 100 µl per well and incubated overnight at 4 ° C at room temperature. The next day, the antigen solution is removed and the plate is washed 3 times with 100 µl of PBS-T20 for each well. The serum samples, previously diluted to ½ with PBS-T20 are added, in volumes of 100 µl / well and then incubated for one hour at 37 ° C.

The serum dilution is removed and washed three times with PBS-T20. Where 100 µl are added per well of dilution of the monoclonal antibody (1: 1000) prepared in PBS-T20 and incubated for one hour at 37 ° C. The antibody is removed by washing with PBS-T20, repeated three times. Thereafter, 100 µl of 1: 1000 diluted conjugate solution per well is added. The plate is covered with self-adhesive tape supplied by the manufacturer and incubated for one hour at 37 ° C. The conjugate dilution solution is removed by repeated washing three times with PBS-T20. A solution of 100 µL of the chromogenic substrate is added and the plate is incubated for 30 minutes at room temperature, protected from light.

100 µL of stop solution is added to each well to observe changes in color and results. The plate is evaluated based on the absorbance reading on an Epoch spectrophotometer (Biotek Instruments Inc.) in the monochromatic form at 450 nm. (Fisher, 2020). This reading then indicates the levels of anti-HCV antibodies present in the patient.

RNA screening using PCR can detect the virus in its initial stage, not necessarily during the chronic disease phase. Detection through RNA can be performed one to three weeks after exposure to the virus, however, it is a more expensive alternative, considering the difficulty of appropriate equipment for screening in different medical centers and liver clinics. (Cresswell et al., 2015).

Recently, tests have been developed that combine viral protein antigens with anti-HCV antibodies, increasing the effectiveness and detection rate in up to 22 days before the conventional ELISA. A disadvantage is the increased cost of this method (El-Emshaty et al., 2011).

The current detection techniques are not a reality for all medical centers and outpatient clinics, making it necessary to develop new detection methods since the technological apparatus for screening HCV-RNA, as well as ELISA is a distant reality for the majority of the global health system.

6. Treatment of Chronic HCV Disease

The treatment of hepatitis C for many years was carried out using a combination based on pegylated interferon-alpha (IFN), conjugated with ribavirin (RBV) (Coppola & Pisaturo, 2015). IFN-based treatment had hepatocytes and lymphocytes as target cells acting through IFN receptors on the cell surface, inducing a response through their receptors, with activation of stimulated interferon genes (ISGs) and antiviral effects (Sasaki, 2015). However, a significant part of human cells has IFN receptors on their surface. This therapeutic combination led to a sustained viral response (SVR) of about 50% in patients with HCV genotype 1, 70% for patients with genotype 2, and about 60% for patients with genotype 3. Due to the low specificity, the treatment resulted in a series of frequent adverse effects, such as flu-like symptoms, depression, cytopenia, and hemolytic anemia, therefore the treatment was very aggressive for patients (Calvaruso, 2012; Coppola & Pisaturo, 2014; Coppola & Pisaturo, 2012). As a consequence of its low specificity, IFN-based treatment easily eradicated mutant viruses that could proliferate in the host. SVR was achieved approximately 24 weeks after the end of treatment (SVR-24) resulting in negative viral loads in patients. An important genetic marker for determining treatment success was the single nucleotide polymorphism (SNP) of Interleukin-28B (*IL-28B*), a factor that contributed to low treatment effectiveness since the prevalence of SNPs is high in the global population (Kanda, 2016).

An important change in the global panorama of the disease has been the development

of an IFN-free therapeutic alternative. A combination of DAAs, with high rates of antiviral response and reduced side effects, allowed the treatment of a wider range of patients, as well as increased SVR rates (about 90%). The new DAAs have been effective especially in patients with difficult treatment, such as cirrhotic patients. These therapeutic agents have a specific action for the viral genome and are administered orally daily. Some of the therapeutic targets for DAAs are viral proteins, NS3 / 4A, NS5A and NS5B. The combination of these protease inhibitors and polymerases is administered, accompanied by ribavirin or not, according to the viral genotype (Kanda & Imazeki, 2010).

In Brazil, treatment is based on sofosbuvir, combined with other DAAs, such as simeprevir and ledipasvir. Treatment regimens last 12 to 24 weeks and may or may not be combined with ribavirin to enhance antiviral action. In more recent data, clinical applications demonstrated an SVR of 87.5% and 92.7% for cirrhotic patients with genotypes 3 and 1, respectively. While for non-cirrhotic patients, SVR was 94.7% and 96.9% for genotypes 3 and 1 (Cheinquer et al., 2017), proving the effective success of this therapy.

A new subtype of genotype 1 has been described in a patient from Equatorial Guinea, with a mutation associated with resistance to NS5A proteins, showing resistance-associated substitutions (RASs) which would make it impossible to treat using the existent DAAs that act on these proteins. The presence of RASs in the HCV genome has been associated with decreased effectiveness of DAAs. Sequencing techniques (Ultra-deep sequencing - Ilumina) can be applied to search for RASs (Kumada et al., 2015).

After eradicating the virus, it is necessary to keep monitoring the disease, especially in patients with advanced degrees of hepatic fibrosis (F3-F4). Non-invasive techniques such as fibroscan may be used to assess the regression of hepatic fibrosis, as well as hepatic and extrahepatic consequences of increased portal pressure. Achieving SVR increases patients' survival curve as well as the quality of life, however, the effects on the risk of developing HCC remains uncertain (Alberti & Piovesan, 2017; El Kassas et al., 2018; Sasaki et al., 2018).

Due to the rise of RASs, the oversight and surveillance of HCV are needed, to develop therapeutic alternatives to counter possible mutant variations of DAA-resistant viruses.

7. Final Considerations

Liver fibrosis and hepatocellular carcinoma are severe clinical consequences of infection by the hepatitis C virus, affecting a significant percentage of the world population.

The development of direct-acting antivirals has considerably increased the control of transmissibility rates, as well as the regulation of disease progression.

However, it remains necessary to monitor post-treatment patients, as well as the treatment of patients who are still affected by the virus, to ensure that there is no progression of liver fibrosis in cirrhosis, nor the development of HCC. Additionally, vigilance should be maintained for possible mutations and the emergence of viral resistance to DAAs.

Thus, further studies are needed to provide a greater understanding of subsequent clinical conditions in the scenario of viral eradication, leading to a decrease in the risk of fibrogenesis and carcinogenesis in these patients.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

This study was supported by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).

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