25 years of Hepatitis C

Parise ER. 25 years of Hepatitis C

HEADINGS – Hepacivirus. Liver cirrhosis.

During the decade of 60 and even 70 medical literature recognized only two types of hepatitis: type A, mainly affecting children, spread often at epidemic levels via food or water contaminated with infected feces and never chronic and type B, with parenteral transmission that could eventually evolve into chronicity, leading to the (then called) post-necrotic cirrhosis\(^1\). After the identification of the Australia antigen (later called surface antigen of hepatitis B, HBsAg) by Blumberg et al.\(^7\) it seemed that the causative agent of parenteral transmission of hepatitis had been found, but it soon became clear that this virus could not be responsible for all cases of post-transfusion hepatitis. When hepatitis A virus was recognized and an antigenic system was developed, it could be associated with the infectious hepatitis. After analysis of many cases of transfusion hepatitis which could not be attributed to the hepatitis virus A or B, cytomegalovirus or Epstein Bar, Alter et al. denominated this disease as non-A non-B hepatitis, and a series of unique epidemiological characteristics were being identified for this hepatitis and its clinical outcomes\(^3, 4\). Finally in 1989, researchers were able to identify an antibody (Anti-HCV) as a marker for hepatitis C and related to different aspects of the disease\(^5, 17\). The identification of this antibody and its rapid implementation for blood and derivatives screening by blood banks, associated with the determination of hepatitis B antigenic system determine dramatic reduction in post-transfusion-transmitted disease in the world\(^17\). However, the damage was already done during the previous years leading up to the discovery of the marker for hepatitis C, millions of people were infected by blood transfusion, use of non-disposable needles and syringes or cutting pierce materials contaminated with hepatitis C.

According to a national study, the prevalence of hepatitis C in Brazil is 1.54% in the adult population (age 20–69 years) and 0.70% in the 10-to-20-year age range\(^8\). Based on the age distribution data of this survey, the current population infected with the hepatitis C virus (HCV) would be in the order of 2 million people\(^15\). Chronic HCV infection follows an asymptomatic or oligosymptomatic course over decades and because of that most infected patients are unaware of their condition and do not look for medical attention. According to DataFolha and Brazilian Society of Hepatology survey performed in 2012 in the main metropolitan areas of the country, only 1/4 of the population of Brazil had already performed the test for hepatitis C\(^32\). As the majority of patients is not identified and treated of the disease, the hepatitis slowly continues to progress and as late the diagnosis of the infection is made, the more likely the patients will be in advanced stages of the disease\(^24\). Hepatitis C is now the second leading cause of chronic liver disease in public hospitals and outpatient care facilities only supplanted by alcohol abuse\(^23\) and the leading cause of hepatocellular carcinoma in Brazil\(^9\), accounting for nearly 40% of all cases diagnosed in the country. As an obvious consequence of these facts hepatitis C is now the main cause of liver transplantation, accounting for over half of all cases of cirrhosis and hepatocellular carcinoma leading to transplantation\(^30\).

Official data from Ministry of Health of Brazil, state that 8,216 patients received treatment within the framework of the National Viral Hepatitis Program in 2004, the year of its creation. This number grew from 2009 to 2011, plateauing in the region of 11,000 patients per year in the last years\(^11\). Even taken in account that 5% to 10% of these cases constitute retreatment of patients that do not responded to previous antiviral therapy, in total, no more than 100,000 patients have already received treatment for hepatitis C in the country. As sustained virological response (SVR) rate could be calculated as no more than 50%, it can be realized that mere 2.5% of the infected population has been cured in Brazil (Figure 1). It bears stressing that, unlike therapy of other viral illnesses, successful treatment of hepatitis C cures the infection, halts disease progression, significantly reduces the risk of developing hepatocellular carcinoma (even in advanced cases) and even reduces non-liver-related mortality, both in patients with HCV infection alone and in the presence of HIV–HCV co-infection\(^1, 6, 18, 35\).

Hepatitis C treatment with interferon was first applied at the time that the disease was called “non A non B hepatitis”\(^18\), and has evolved since then.

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\(^{2}\) President Brazilian Society of Hepatology. Assistant Professor Gastroenterology-Hepatology Section of Federal University of São Paulo.

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The incorporation of ribavirin and, in the last years, of first
generation protease inhibitors (telaprevir and boceprevir)
have increased significantly the numbers of respondents to
such antiviral therapy at same time that increased the number
and the gravity of the adverse events as demonstrated by
Almeida et al. in this issue of ARQA[2]. Despite the limited
number of patients studied, which prevents any considera-
tion about the virological response rate, it portrays the higher
rate of complications seen with this therapy, with almost
60% of patients with anemia and early discontinuation of
treatment in more than 30% of patients. These numbers
were much higher than the observed with dual therapy (peg-
interferon and ribavirin), and are in accordance with data
from the most important real-life study with triple therapy,
the French Cupic Study[16]. The DAA second generation
(sofosbuvir, simeprevir and daclatasvir), in the opposite
direction, with the possibility of combining themselves and
avoiding pegilated interferon are able to significantly reduce
the extension and the complexity of the treatment and the
incidence of side effects, in parallel with a rate of SVR near
80%-90% for all genotypes[27]. Although extremely important,
this achievement is not enough. If the number of patients
receiving antiviral therapy stays the same, the expectation
for the coming years is of an important increase in the
number of chronic hepatitis C complications as cirrhosis
and hepatocellular carcinoma, with increase in medical costs
for the public and private sector[28]. In order to have a great
impact on hepatitis C burden it will be necessary to increase
both diagnosis and access to treatment. In the detection of
 carriers of this virus, it is important to modify the standard
used so far to their identification by prioritizing those with
parenteral risk factors (blood transfusion, hemodialysis, etc.).
About 70%-75% of patients infected by hepatitis C virus in
our country is aged more than 40-45 years[13, 24, 31]. Individu-
als in this age group must be consider at risk and tested for
hepatitis C, regardless of whether they have a history of
blood transfusions, have made use of disposable syringes and
needles, or exposed to other forms of contamination. This
strategy proved to be superior to conventional methods in
the detection of hepatitis C[10, 29]. In this issue of the Archives
of Gastroenterology, Oliveira et al. assessed the prevalence
of hepatitis C in Paulista University (UNESP) employee in
total more than 3000 people[25]. Despite the low prevalence
observed (0.7%) for hepatitis C in such population, they were
able to confirm that those older than 40 years of age are at
more risk to be contaminated with HCV virus. Additionally
the authors call attention to factor overlooked by younger
doctors in epidemiological studies, which is the use of non-
disposable syringes and needles in the past. It is specially
mentioned the application of energetic stimulant (Gluco-
energan®) often formerly used by revelers at Carnival or by
athletes that is responsible for several cases of hepatitis C in
these populations[33]. Increase access to treatment is another
important task getting rid of the barriers that prevent the
patient to have their treatment[34]. Expedite the diagnosis with
rapid serological tests and staging of disease with noninvasive
tests in place of liver biopsies, use of more effective drugs
with safer treatments, with lower rates of adverse events are
important part of this equation. But doctors from other
areas beyond the hepatologists and infectious disease spe-
cialists will be needed in this fight against hepatitis, and the
gastroenterologists are among them. Therapeutic simplicity
in the use of new coming drugs (as those to be approved by
ANVISA in 2015) in antiviral therapy will allow the gastro-
enterologist not affect the treatment of hepatitis to join the
efforts against hepatitis C.

In this special issue of the Archives of Gastroenterology,
we have another interesting article on hepatitis C addressing
the beneficial effects of caffeine in the evolution of this liver
disease[26]. It has long been aware of the beneficial effects of
coffee on serum liver enzymes and the alcoholic liver disease,
but since 2009 several studies have shown that caffeine intake,
especially in the form of coffee, has a protective effect on the
development of hepatitis C virus[12, 14, 21, 22]. In our previously
published study[27], we observed a reduction in liver fibrosis
in patients taking higher doses of caffeine in univariate and mul-
tivariate analysis when compared to patients with lower daily
intake of caffeine, but did not observe a relationship between
caffeine with inflammatory activity in liver biopsy. We drew
attention fact that the amount of caffeine necessary to reduce
the degree of fibrosis was significantly lower than in English
literature (125 mg or only 4 Brazilian cups of coffee versus
250 mg or 308 mg daily). This difference can be attributed
to several factors but interestingly, in our population coffee
represented more than 90% of the daily caffeine intake, while
in other studies a large contingent of caffeine derived from
soft drinks and processed juices[12, 14, 21]. The study of Oliveira
et al. confirms our findings of the relationship between lower
grade of fibrosis and the ingestion of higher doses of caffeine,
although this association was not find in multivariate analysis.
The cutoff value for caffeine used was the traditional (250 mg)
and although certainly researched, it was not report in the

FIGURE 1. Effectivity of hepatitis C diagnosis and treatment in Brazil.
article the origin of calculated amount of caffeine. It should be remembered that in the South of Brazil there is another form of caffeinated beverage that is the use of mate infusion (“chimarrão”), and it would be interesting to know whether this had any impact in caffeine ingestion in this study. Also like in our study, there was no association between the amount of caffeine and the inflammatory activity in the tissue, suggesting that this protective effect could be relate to the fibrogenic activity of the tissue, but this would be a speculation far beyond the purpose of the studies presented.

Thus, when we complete 25 years of hepatitis C, witnessing one of the fastest and unprecedented advances in the history of medicine in the diagnosis and effective treatment of a disease, is important not to lose focus if we are to make a difference to health policies in this country no impact will be achieve only with excellent medicines. Even with drugs that reach 95% SVR we only effectively will reduce the future impact of the disease if we treat at least 70% of infected patients. It is not yet time to celebrate it’s time to roll up our sleeves and go to fight.

Edison Roberto PARISE*


REFERENCES