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Chronic hepatitis C is still a problem for the public health care system in Brazil

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Globally, about 80 million people are living with the hepatitis C virus (HCV)[1]. In 2016, the World Health Organization (WHO) adopted the Global Health Sector Strategy on Viral Hepatitis to eliminate hepatitis by 2030[2]. This commitment was proposed in response to the growing prevalence of chronic viral hepatitis worldwide The burden of the disease includes direct medical expenses for its hepatic and extrahepatic manifestations, as well as indirect costs related to impaired quality of life and loss of work productivity.

In Brazil, the Public Health Care System has been providing antiviral treatment for chronic hepatitis C for more than a decade with pegylated interferon and ribavirin. This now-outdated treatment, besides high costs, low efficacy, and prolonged duration, could not be administered in several clinical conditions, such as advanced cirrhosis (Child B and C), patients on the liver transplant waiting list (MELD>15), or after any type of organ transplantation. According to global and national recommendations, antiviral therapy could be prescribed only for patients with progressive fibrosis (F≥2). Special groups such as people with HIV/HCV coinfection, renal failure, people who inject drug, children, and others either went untreated or achieved less efficient outcomes.

The great advantage of all-oral treatment with direct-acting antivirals (DAAs) is the possibility of getting rid of interferon/ribavirin regimens, eliminating its adverse effects and achieving greater efficacy. DAAs also created the possibility of treating a wider range of patients, enabling a global campaign for HCV elimination despite the absence of a vaccine. The combination of preventive measures with a very efficacious treatment makes elimination an achievable goal, especially in countries where a public health system is aware of the problem and takes responsibility for addressing it.

In this volume, Minme et al. publish the article "Profile of patients with chronic hepatitis C in a public health program in Southern Brazil"[3]. The authors conducted a retrospective analysis of the main characteristics of 1,431 HCV patients listed for DAA therapy from 2015 to 2016. This is a huge population, the largest of the three publications on hepatitis C presented in this issue. The aims of the three studies are different, and we have chosen to comment on them in order of complexity and increasing interest.

Concerning sex and age, findings were comparable across different regions of the country. Men predominated in all regions and mean age ranged from 56 to 57.8 and 58.6 years, a somewhat older population than in previous Brazilian studies[4,5]. The period of analysis of the three articles covers 2014 to 2016 – the end of the interferon era and the start of the new all-DAA era. The predominance of cirrhosis was also a common factor in all three studies; one, in fact, included only cirrhotic patients. (This serves as a warning to readers, who should interpret these data with caution regarding the patients with early hepatitis C with little or no fibrosis).

The aim of Minme et al. was to present a profile of chronic hepatitis C in Southern Brazil. As geographical and regional differences, related to prevalence and some characteristics of hepatitis C, are well known around the world, it is valid to evaluate them in a very large regional case series. The take-home message of the article was that, although genotype 1 was predominant (60.5%), a high percentage of genotype 3 was found (33.8%) as a unique regional characteristic of the Brazilian South. Studying associations, the authors also found a greater prevalence of F4 (cirrhosis) in patients with genotype 3 and a higher viral load in those with genotype 1.

In this volume, Silva et al. publish the article "Waiting DAAs list mortality impact in HCV cirrhotic patients"[6]. The authors have followed a cohort of 129 patients with HCV cirrhosis for 11.2 months while on a waiting list for treatment with DAAs. During this period, the lethality rate was 6.9%, corresponding to the natural history of the disease. Risk factors for death were serum albumin level <2.9 g/dL, MELD score >15 and α-fetoproteins >40 ng/mL. Other factors, such as increased bilirubin levels, presence of ascites, bleeding esophageal varices or blood dyscrasia (measured by high INR) were not shown to be independent risk factors for death in this Brazilian cohort.

These data are particularly relevant because knowledge of the natural history of HCV is the cornerstone of any evaluation of the need for therapy and serves to justify the high costs of antiviral treatment. Here, the question is not about the progression of chronic hepatitis C to cirrhosis, but a possible modification of its natural course, once cirrhosis is fully installed. Besides raising the issue and providing some clues, the authors also open new perspectives for important future researches. There is a pressing need to stratify patients with cirrhosis (of any etiology), since prognosis is extremely variable. Besides the Child-Pugh classification and the MELD score, there is also another very simple and easily applicable stratification available. The BAVENO´s prognostic score considers the presence of varices, ascites, bleeding due to portal hypertension or the combination of other clinical complications related to portal hypertension[7].

The second point that must be highlighted is that antiviral treatment leading to SVR (sustained virological response) in patients with established cirrhosis may not only prevent complications, but also contribute to fibrosis regression[8]. On the other hand, follow-up of these patients is mandatory due not only to possible onset of hepatocellular carcinoma but also because, in more advanced cases, the disease may progress despite treatment and complications of cirrhosis develop[9].

In this volume, Castelo et al. publish their investigation "Hepatitis C in the Brazilian public health care system: burden of disease"[10]. In this multicenter study, the authors enrolled 313

patients with chronic genotype-1 hepatitis C. All grades of fibrosis (0–4) are covered, although the majority (42.8%) of patients had cirrhosis (F4). To evaluate disease burden, Castelo et al. used three questionnaires – the EQ-5D-3L, HCV-PRO, and WPAI:Hep C – to assess quality of life, functional status, and well-being. The EQ-5D-3L is a generic instrument assessing health status on five domains, whereas the HCV-PRO is a specific instrument to measure the effects of disease on function and well-being. The WPAI:Hep C questionnaire is designed to measure the effects of hepatitis C on productivity in the workplace and beyond. Comorbidities were highly prevalent in this cohort, with cardiovascular disease in 62.6% and metabolic disease in 50.5%. The leading complication of hepatic disease was presence of esophageal varices (54.5%), although bleeding from varices was present in only 7.3% of patients and hepatocellular carcinoma was diagnosed in a similar number of cases (7.3%). The questionnaires showed that anxiety and depression (53.9%) as well as pain and discomfort (47.5%) were very frequent. Productivity was the most commonly affected component of daily activity, affecting 23.5% of patients.

The key message of these data is extremely clear. Chronic hepatitis C, although apparently silent and most of the time asymptomatic, is associated with various and serious comorbidities and compromises health-related quality of life, as previously demonstrated[11]. Besides re-enforcing this often overlooked aspect, the authors evaluated medical costs, most of them covered by the Public Health Care System. The price of anti-virals corresponded to 95% of medical costs in the sample. As mentioned by the authors, the period of study corresponded to the advent of triple therapy with first-generation DAAs (telaprevir or boceprevir), just before the all-oral second generation of DAAs became available. At the time, severe treatment-emergent adverse reactions were still common and SVR rates were still low, around 65% to 70%. Soon after, starting in the end of 2015, all-oral combination treatment with DAAs achieved a real-world efficacy greater than 90% in Brazil. Side effects now tend to be mild, if present at all, and the mean duration of treatment has been shortened from 12 to 3 months.

Curing HCV infection is the first step to stopping the progression of liver disease. When this is achieved only after the onset of cirrhosis, patients must be staged and perspectives for regression of fibrosis is possible in less compromised patients. Conversely, development of hepatocellular carcinoma must be continuously evaluated. From this perspective, the cost burden of the disease cannot be limited to the time frame of antiviral treatment; a longer period of observation (years or decades) is desirable.

In Europe and United States DAAs became available 2 years before their launch in Brazil and clinical researches are already showing the good results of the new "elimination policy" for HCV hepatitis. A particularly good example is the transplant field, where fewer cases of decompensated HCV cirrhosis are being listed for liver transplantation. In Italy, an evaluation of 1,109 patients waitlisted for transplant before and after the introduction of DAAs revealed a significant decrease in HCV-related cirrhosis, especially for decompensated forms (from 24.2% to 15.9%)[12]. Similar results were found in a Spanish study of 2,379 patients waitlisted for liver transplant due to decompensated hepatic disease, with a significant decrease over time with large-scale use of DAAs[13]. More recently, a multicenter study including various European countries and the United States enrolled 60,527 liver transplant cases. Besides a decline in listing of patients with HCV-decompensated cirrhosis, the authors observed that post-liver transplant survival for HCV patients improved over the last 3 years due to the impact of DAAs[14].

Cost-effectiveness is an especially relevant issue in the treatment of hepatitis C, due mainly to the high cost of antiviral therapy, as noted by Castelo et al.; a growing body of research on this problem is being published worldwide. Some authors have described clinical, economic, and quality-of-life benefits[15]. In the first 5 years post-treatment, medical costs for patients achieving SVR are 13-fold lower than for patients not achieving SVR[16]. Different approaches for the cost-effectiveness analysis of hepatitis C treatment with DAAs were the subject of a recent systematic review of 36 publications, mainly from Europe and the U.S. Cost-effectiveness was largely rated as acceptable, from 67% to 100%[17].

In a Brazilian study of real-life cases of hepatitis C treated according to the Brazilian protocol of HCV treatment (PCDT), treatment costs for genotype-1 HCV patients were found to vary over time. Triple therapy with association of IFN/Riba and the first generation of DDAs was the most expensive whereas the new interferon-free regimens all-DAAs of second generation being the least expensive[18].

Although new treatment strategies yield excellent results in terms of efficacy and control, new problems have emerged and must be dealt with judiciously. The first one is the possibility of development of mutant HCV strains, which occur in patients who fail to achieve SVR. These may be related to the type of drug used or treatment period according to genotype, and usually occurs in the NS5A or NS3/4A regions of the HCV virus[19]. Nevertheless, recent clinical trial data show that most patients who fail HCV treatment with DAAs have excellent retreatment options since newly approved salvage therapies have become available[20].

In order to reduce the burden of chronic hepatitis C and improve treatment outcomes, the populations most difficult to treat or cure – such as those co-infected with HIV and people who inject drugs (PWID) – deserve specific measures to reduce ongoing exposure. Reinfection after successful HCV treatment is an important public health issue, and may impact efforts to control HCV transmission. As these groups usually went untreated, rates of HCV reinfection were low and seldom described in the interferon era; but now, with the advent of DAAs, these percentages have risen. In a recent study of 4,114 individuals, HCV reinfection was found to occur in 5.7% and 10.2% of recent PWID and patients with HCV-HIV co-infection. The authors of this remarkable and interesting study suggest multicomponent prevention strategies, such as continuous opioid-agonist treatment (OAT) for PWID following the end of successful DAA treatment, as reinfection was found to occur in only one patient on daily OAT[21].

In conclusion, cure of chronic hepatitis C is real and possible. There is a long way to go and plenty of hard work ahead on the road to 2030; Brazilian physicians must focus on treating as many HCV-infected patients as possible and on controlling HCV transmission. With the support of a strong and cooperative public health care system, this ambitious objective can be achieved.

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