PERSPECTIVE

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Hepatitis c virus, still around after all these years: Enough is enough

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Viral hepatitis. New light on an old disease was the title of an article published by Saul Kurgman in 1970, almost 50 years ago, in the *Journal of the American Medical* Association[1], on an unknown viral agent that seemed to cause hepatitis.

Later, in 1974, in an article published in the *Lancet*, Prince and colleagues[2] reported that an agent other than the hepatitis-B virus seemed to be the cause of 36 (71%) of 51 cases of post-transfusion hepatitis identified during prospective biweekly serological follow-up of 204 cardiovascular-surgery patients. The authors concluded that a large proportion of long-incubation post-transfusion hepatitis is unrelated to hepatitis B and that control of post-transfusion hepatitis will require identification of a hepatitis virus(es) type C. Since then, there has been little interest in the topic hepatitis C. It was only in 1988 that workers at Chiron Corporation discovered a viral antigen specific for post-transfusion non-A, non-B hepatitis that was termed hepatitis C virus (HCV), with this discovery published in *Science* in 1989[3].This finding allowed the development and availability of a serologic test for detection of the HCV antibody for clinical use.

The first human intervention for chronic hepatitis C, interferon given three times per week subcutaneously, appeared in 1986 but this therapy only induced persistent remissions in about 6% of the patients. For example, Davis and colleagues[4], studying 166 patients with chronic post-transfusion non-A, non-B hepatitis, showed normal or near-normal serum alanine aminotransferase (ALT) levels in 46% of patients treated with interferon alfa-2B for six months compared with 8% of untreated controls, but the discontinuation of therapy was associated with a high rate of relapse, as shown by elevated ALT levels. Fifty-one percent of responding patients had relapsed by six months.

In 1995, double therapy with interferon plus ribavirine became the standard of care for all HCV genotypes, and was associated with improved efficacy as compared with interferon alone, as 40% to 50% of patients showed a sustained virologic response (defined as an undetectable HCV RNA level 24 weeks after cessation of antiviral therapy).

The molecular characterization of the virologic features and life cycle of HCV has led to the development of directly acting antiviral agents (the protease inhibitors telaprevir and boceprevir) in 2011[5,6]. With the initiation of triple therapy with pegylated interferon (peginterferon) in combination with ribavirin and boceprevir or telaprevir, treatment efficacy (evaluated by the proportion of patients with sustained virologic response) has increased to about 70%, but only for genotype-1 infected patients.

However, although the use of the triple therapy with directly acting antiviral agents (DAA) increased the proportion of patients with sustained virologic response, it was still associated with several huge problems, namely, the need for the use of interferon, ribavirin, and DAAs, drugs with a high incidence of adverse effects, including depression, anaemia, thrombocytopaenia, neutropaenia, serious cutaneous rash and so on.

But now, in 2016, the paradigm has changed dramatically as there is no longer a need for interferon, boceprevir, or telaprevir. Furthermore, liver biopsy has been replaced in more than 90% of cases by elastography (FibroScan). It is now possible to assess fibrosis of the liver by this method, which is similar to an

ultrasound, taking only two minutes to perform, and there is no need for hospital admission. It is very easy for the operator to learn as he/she needs to perform only 50-100 examinations to be able to do it routinely. Elastography has been used in Portugal since 2005. Therefore, the management of hepatitis C is currently needle-free: no need for liver biopsy and thus no need for a needle to be inserted into the liver to collect a tissue sample; no need for injections to administer interferon.

Directly acting antiviral agents are currently the gold standard of HCV treatment. The World Health Organization[7] has included these medications on the list of essential medicines. The new treatments are oral drugs with acceptable side effects and include sofosbuvir, sofosbuvir + ledipasvir, daclatasvir, simeprevir, paritaprevir + ombitasvir + dasabuvir, and grazoprevir + elbasvir. Velpatasvir (already approved by the Food and Drug Administration of the US and the European Medicines Agency), in association with sofosbuvir and sometimes ribavirin, showed pangenotypic effectiveness, and seems to be the herald of a new era.

The recommended regimens for patients with severe renal impairment (creatinine clearance lower than 30 mL/min) or End-Stage Renal Disease (ESRD) requiring haemodialysis or peritoneal dialysis are variable according to the genotype. The medications that can be used are only paritaprevir + ombitasvir + dasabuvir, and grazoprevir + elbasvir. Ribavirine is still needed in about a quarter of cases but in renal patients must be used in a dose-adjusted way (200 mg daily). The treatment of hepatitis C in renal transplant recipients with direct-acting antiviral agents is almost always successful.

The most updated international guidelines are those drawn up in collaboration with the American societies, the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (ISDA). The last report dates from 16th September 2016[8].

The burning question is how to manage HCV infection in patients with renal impairment, including patients requiring haemodialysis or peritoneal dialysis. First, as all patients must be considered infectious, the precautions for avoiding the transmission of HCV and other viruses should be universal. But if we think of HCV eradication in this group of patients, or reducing the HCV burden in terms of public health, all patients should have access to the best treatments, starting with the new DAAs. No vaccine is expected in the near future. The efficacy of DAAs, not only in clinical trials, but also in real life, has been around 95%. In Portugal, access to medication is universal, and its efficacy, as evaluated by proportion of patients with remission, was 96% (Figure 1).

WHY TREAT?

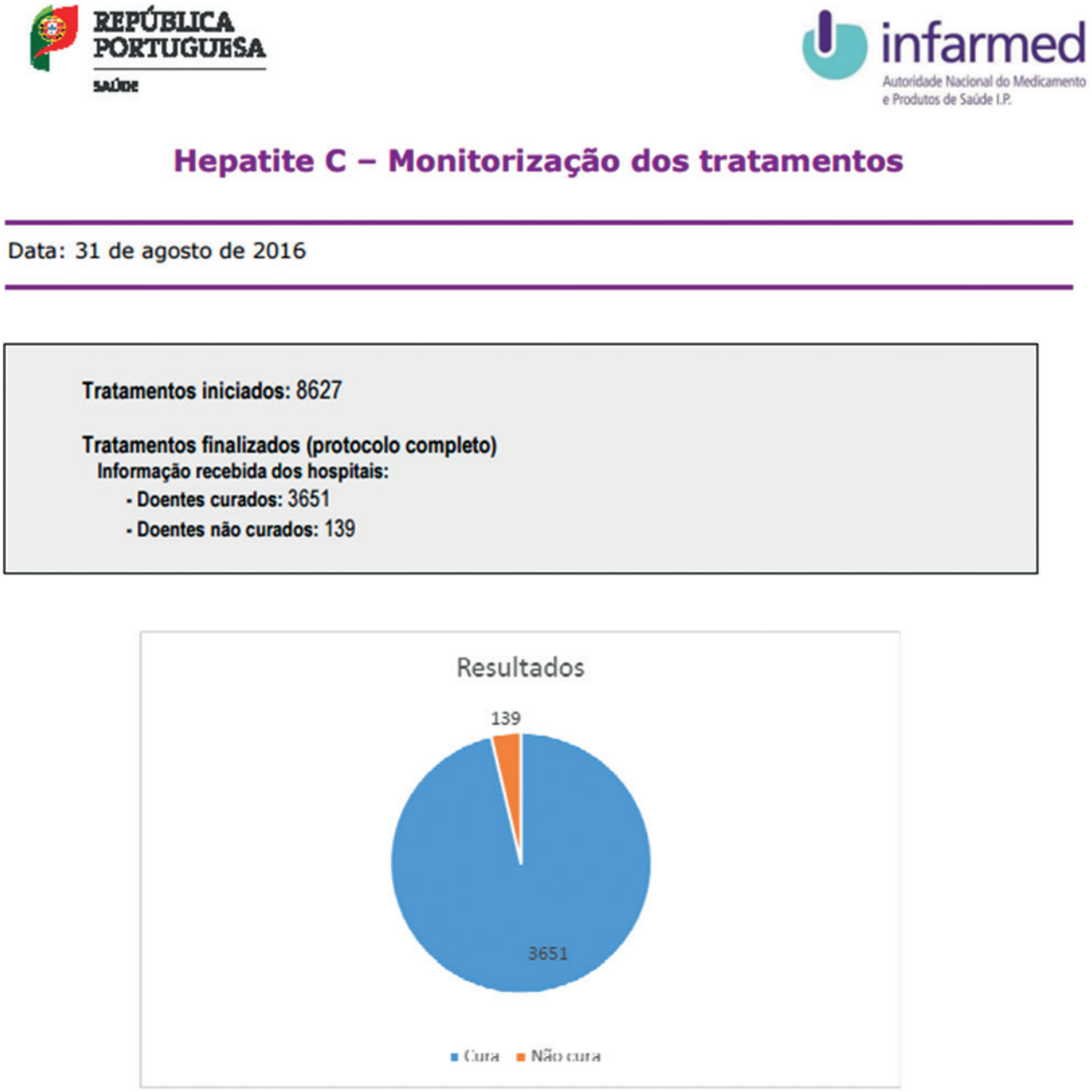
The benefits of HCV treatment are huge, even in patients with (supposed) mild grades of fibrosis[9]. Liver biopsy or elastography has an accuracy of 80% in the diagnosis of cirrhosis. Therefore, 20% of patients have a wrong classification regarding their fibrosis, in general false negatives. HCV is at the same time a contagious disease, a liver disorder, a stigma, a disease competing for a liver transplant, a dying patient needing palliative care, etc. Additionally, chronic hepatitis C is a burden to the individual, family, and society in general. So, why not interrupt the chain? HCV is an oncogenic virus. The risk in patients with cirrhosis of developing hepatocellular carcinoma is around 10-40% after 10 years of disease. Nowadays, the percentage of patients with cirrhosis in Portugal is 36-49%, depending on the genotypes. The higher percentage of cirrhosis is in genotype 3. In patients with mild fibrosis, directly acting antiviral agents have been proven to reduce the risk of evolution to cirrhosis. In some patients with more severe fibrosis, the cirrhosis can even disappear. Around one fifth of patients with decompensated cirrhosis, already on the waiting list for liver transplant, can be taken off the list. The risk of evolution to hepatocellular carcinoma is reduced on a long-term basis; the oesophageal varices can disappear and, in many of cases, liver elastography returns to normal values; the score for the evaluation of quality of life improves in all aspects; sexual transmission and vertical infection is interrupted, and so on. Why not treat? The only reason would be economics, but in Portugal this has been solved, since February 2015. The treatment has no major contra-indications.

HOW TO TREAT?

How to make a correct diagnosis? Firstly, look for antibodies to HCV in all patients on dialysis. If patient is positive for antibodies to HCV, look for HCV RNA by PCR. If patient is positive for HCV RNA, then the patient has chronic hepatitis C. In which case an abdomen ultrasound, an elastography (Fibroscan®) and general blood tests, including HCV genotype, should be

Figure 1

Monitoring hepatitis C treatment in Portugal. Data from INFARMED (National Authority of Medicines and Health Products, a government agency accountable to the Health Ministry): 8627 patients have begun treatment, 3651 have finished treatment, and 3651 patients have sustained virological response. Portugal is one of the few countries worldwide to give free treatment to all HCV-infected patients.



performed. At this point, the collaboration of physicians with experience in dealing with patients with chronic liver disease should be sought (gastroenterologist, hepatologist, infectious disease specialist or internal medicine specialist). These physicians, after confirming the virus genotype, can prescribe the treatment on the INFARMED website. (http://hepc.infarmed.pt/(S(yo4peqwnvidiai2vfl40c5ea))/Login.aspx). If approved, the patients can have access to medication in around one-two months. In general the treatment can last 8-24 weeks. The great majority lasts for 12 weeks. Half of the patients become HCV RNA negative

at 2 weeks and less than 1% has clinically significant side effects. Patients CHILD B or C in general should not be treated, or should only be treated in a liver transplantation unit.

WHO CAN TREAT PATIENTS?

Only doctors with experience in dealing with chronic liver diseases should treat these patients as almost half of the patients with chronic hepatitis C already have liver cirrhosis. Furthermore, physicians should have experience in dealing with decompensated liver cirrhosis, which is a possible complication in this setting, and be aware that liver cirrhosis is a risk factor for hepatocellular carcinoma. For these reasons, it is recommended that patient with chronic hepatitis C perform an ultrasound every 6 months for life.

WHEN TO TREAT?

Patients should be treated as soon as possible. Chronic hepatitis C is not a medical emergency, but why not treat? The risk of appearance of hepatocellular carcinoma in patients with cirrhosis is 0.5% to 2% at six months, not a negligible one.

WHAT ABOUT CURE?

If the patient has no cirrhosis (sensitivity of elastography is around 80%), he can be discharged from the liver outpatient clinic when HCV RNA is negative 12 weeks after stopping the antiviral therapy. Patients with cirrhosis need to be reassessed every 6 months during a medical visit, with an abdominal ultrasound included in this assessment. The percentage of patients that remain RNA HCV negative after the first negative test is around 99.9% or more.

In conclusion, to treat chronic hepatitis C with the new DAAs is a strong contribution to eradicating the disease in renal patients. In doing so, we can help many of the Portuguese patients and their families by abolishing the risk of transmission of an oncogenic virus, reducing the risk of evolution to cirrhosis and to hepatocellular carcinoma, as well as the need for liver transplant, and reducing morbidity and mortality[10]. Within a timeframe of less than 6 months we have the tools to do all of this in 96% of cases. This is the first time that man has been able to cure a chronic and oncogenic viral infection within a 12-week period in most of the patients treated.

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