

Elimination of Hepatitis C in Portugal: An Urban Legend?

José Velosa^{a, b} Guilherme Macedo^{c, d}

^aGastroenterology Department, Centro Hospitalar Lisboa Norte, Lisbon, Portugal; ^bFaculty of Medicine, University of Lisbon, Lisbon, Portugal; ^cGastroenterology Department, Centro Hospitalar e Universitário São João, Porto, Portugal; ^dFaculty of Medicine, University of Porto, Porto, Portugal

Keywords

Hepatitis C · Micro-elimination strategies · Public health

Abstract

The burden of hepatitis C virus infection remains very high despite huge progress in the cure of the infection. The high prevalence of hepatitis C, especially in vulnerable groups and particularly drug users, may compromise the achievement of the 2030 WHO targets with a 90% reduction in new infections and a 65% reduction in mortality. Therapy with the latest pangenotypic direct-acting antivirals provides cure rates in the order of 97% with short-term oral treatment (8–12 weeks) and with an excellent safety and tolerability profile. Curing the infection causes significant health gains derived from preventing complications from cirrhosis, especially hepatocellular carcinoma, and from liver transplantation. Elimination of hepatitis seems feasible with the implementation of a massive therapy program, focusing particularly on vulnerable populations, through micro-elimination strategies, and in the general population with age-based screening. The reduction of the virus reservoir (humans are the only reservoir) is a determining factor in eradicating the virus.

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Palavras Chave

Hepatite C · Estratégias de microeliminação · Saúde publica

Resumo

O peso relativo da infecção pelo vírus da hepatite C permanece muito elevado apesar dos enormes progressos verificados na cura da infecção. A elevada prevalência da hepatite C, sobretudo nos grupos vulneráveis e em particular nos utilizadores de drogas, pode comprometer o atingimento das metas da WHO para 2030 com redução de 90% de novas infecções e redução de mortalidade em 65%. A terapêutica com os antiviricos de acção directa mais recentes, pangenotípicos, proporciona taxas de cura da ordem dos 97% com tratamento oral de curta duração (8–12 semanas), e com excelente perfil de segurança e tolerabilidade. A curada infecção ocasiona significativos ganhos em saúde derivados da prevenção das complicações da cirrose, sobretudo do carcinoma hepatocelular, e do transplante hepático. A eliminação da hepatite parece

exequível com a aplicação de um programa de massificação da terapêutica, incidindo particularmente nas populações vulneráveis, através de estratégias de microeliminação, e na população geral com rastreio baseado na idade. A redução do reservatório do vírus (o homem é o único reservatório), é determinante para a sua eliminação.

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Introduction

Chronic hepatitis C virus (HCV) infection is a worldwide disease. The viremic population is estimated at 71.1 million, corresponding to a global prevalence of 1% [1]. In 2015, the prevalence of viremic HCV infections in the EU was estimated to be 3,238,000, corresponding to a prevalence of 0.64% [2]. The Polaris study [1] estimated that the infected population was 1.2 million in Central Europe, 2.3 million in Western Europe, and 6.7 million in Eastern Europe in 2015. Mortality resulting from complications of the disease is 500,000/year globally, out of which 70,000 occur in Europe [3, 4]. Epidemiological data for Portugal are not up to date, especially regarding the prevalence of viremic patients. Two recent studies found an anti-HCV prevalence of 0.54% [5], of 0.65% in the general population and of 2.3% in the population consisting mainly of people who inject drugs (PWID) [6]. The decline in the prevalence of viremic patients, other than HCV antibody seroprevalence, is a reality that shows the spontaneous cure of acute and posttreatment infection, and a reduction in mortality associated with complications of the disease.

In the Western world, HCV infection is particularly prevalent in vulnerable populations, particularly drug users [7]. From an epidemiological and treatment-strategic point of view, it is important to distinguish active drug users (PWID) from past drug users. The former are the target of hepatitis C micro-elimination programs implemented around the world [8], whereas for the latter, a macro-elimination strategy is advocated based mainly on universal screening or age-based cohorts [9]. For different reasons, some epidemiological factors have been pointed out in Portugal that could explain a higher prevalence in older age groups, namely, baby boomers [10].

The gradual increase in liver fibrosis over the years characterizes the natural history of hepatitis C, with a 20% risk of cirrhosis developing after 20 years of infection. In patients with compensated cirrhosis included in screening programs, hepatocellular carcinoma is the first complication, followed by liver decompensation and death

[11]. In Western countries, HCV accounts, respectively, for 38 and 44% of cases of cirrhosis and hepatocellular carcinoma (US CDC); patients with hepatitis C-associated cirrhosis represent the largest fraction of cirrhotic patients undergoing liver transplantation: about 35% in the USA [12], and 13%, on average, in Europe [13].

The bleak outlook of hepatitis C [14, 15] has completely changed since 2011, with the introduction of the first direct-acting antivirals (DAAs). The cure of this infection has become a reality in almost all treated patients, and the resulting benefits are already evident: a reduction in the prevalence of cirrhosis and complications associated with cirrhosis, as well as a decrease in the prevalence of hepatocellular carcinoma, in mortality, and in the number of liver transplants [16, 17]. With the advent of DAAs, the number of transplants due to hepatitis C-associated decompensated cirrhosis has declined by 50 and 40% in Europe and the USA, respectively [18, 19].

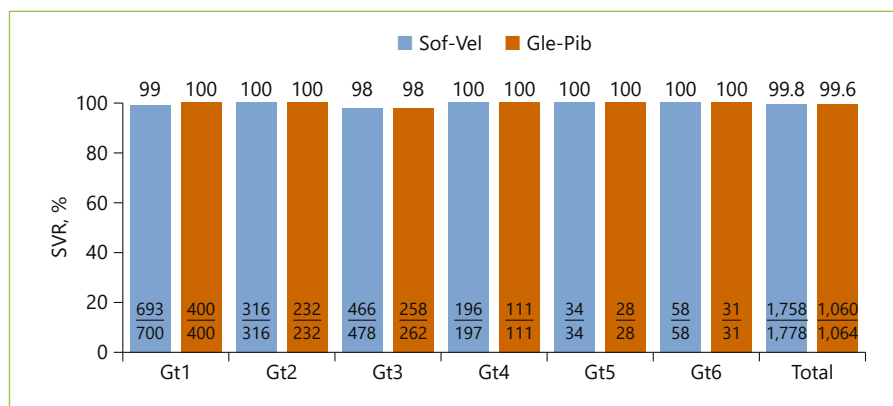
Following the deliberation issued in 2015, the WHO published in April 2017 a report outlining a strategy for a 90% reduction in the incidence and a 65% reduction in the mortality of hepatitis C by 2030 in Europe [4]. In November of the same year, it redefined the recommendations for the elimination of hepatitis C in Europe [20]. However, there is a general conviction that to achieve these goals, it is necessary to implement a strategy that combines screening with prevention and treatment [21].

In 2015, Portugal was one of the first countries in the world to approve universal access to hepatitis C treatment, and there were a significant financial impact and health gains in the first year of implementation of the program [22]. Unfortunately, data beyond 2015, when treatment has been implemented on a large scale, are not yet available, and most EU countries have adopted effective HCV elimination programs.

Efficacy of Antiviral Therapy

Following the introduction of DAAs 8 years ago, hepatitis C therapy has evolved dramatically. With the latest pangenotypic drugs, about 97% of patients can be cured with a tablet a day, for 8–12 weeks, regardless of genotype, disease stage, and previous therapeutic experience [23–25]. The effectiveness and safety of the DAAs allow the simplification of the therapy, doing away with the on-treatment monitoring, except proof of viremia before and after treatment. There is nearly a broad consensus among experts that the elimination of hepatitis C by means of antiviral therapy, a process unheard of in the history of

Fig. 1. SVR (cure) within 12 weeks of treatment in patients treated with sofosbuvir-velpatasvir (Sof-Vel; Epclusa®) and glecaprevir-pibrentasvir (Gle-Pib; Maviret®). SVR, sustained virologic response; Gt, genotype.



infectious diseases, needs to be combined with preventive measures to reduce the infection transmission.

Several observational studies have shown a reduced risk of hepatocellular carcinoma, complications of cirrhosis, and mortality in treated patients who have achieved cure of the infection, either with interferon [17] or with DAAs [26–28].

Barriers to treatment, which in the past were mainly related to the adverse effects of interferon, still exist today, now due to reasons other than drug efficacy and tolerability. Table 1 lists a number of reasons why in 2015 only 7% of the world’s diagnosed population received treatment [3] and only 12.7% in the EU [2]. Treatment rates are very likely to be even lower in vulnerable populations, traditionally negatively discriminated against in the access to DAAs; in the opinion of the Fifth International Viral Hepatitis Elimination Meeting (IVHEM), lack of funds still is the main barrier to the elimination of hepatitis C [29]. Indeed, the cost of DAAs, despite the significant reduction in price, remains paradoxically one of the biggest obstacles to treatment in high-income countries [3]; nevertheless, the common reluctance to provide institutional healthcare, the bureaucracy, and some bias in accessing to and dispensing of DAAs to minorities are probably the biggest obstacles to eliminating hepatitis C [30, 31].

Elimination of Hepatitis C

Given the great efficacy and simplicity of the therapy, the WHO and many experts believe that it is possible to eliminate hepatitis C using antiviral treatment [20] – especially now, when pangenotypic DAAs provide a greater chance of cure and dose uniformity in different patient groups [25]. From an infection elimination perspective, it is just as important to treat those infected as preventing new infections

Table 1. Barriers to treatment of hepatitis C

- To identify undiagnosed individuals (lack of diagnosis)
- High cost of medications (affordability of HCV treatment)
- Reluctance of people who inject drugs to attend specialty clinics to access treatment
- Difficult linkage to care and retention in care
- Access to national health and insurance services among migrant populations
- Confirmatory HCV RNA testing (a rapid test or HCV core antigen testing – point-of-care testing)
- To assess the extent of liver fibrosis
- Restrictions on the eligibility of prescribers
- Demanding on-treatment monitoring strategies
- Difficult access to medication due to heavy bureaucracy
- Absence of official strategic plans
- Lack of information at all levels of the cascade of care

from occurring. In order to achieve this goal, it is necessary that the number of patients cured every year is greater than the number of new infections, and it is not clear that this is the case [32]. In Portugal, a recent innovative strategy for micro-elimination was launched in prisons, with a remarkable success rate of 100% of sustained virologic response in this vulnerable patient population [33].

Prevention of New Infections

The WHO advocates a 90% reduction in new infections by 2030 [32]. Given that humans are the sole reservoir of the virus, the focus of prevention should be directed primarily to groups at high risk of infection, especially PWID. Safe syringe programs, safe injection rooms, and opiate substitution therapy are well-established prevention measures [34] and complementary to HCV treatment [31]. Antiviral therapy has a high priority for these persons, as much as repeat screening and renewed treatment of reinfection (Fig. 1). The fear of poor adherence

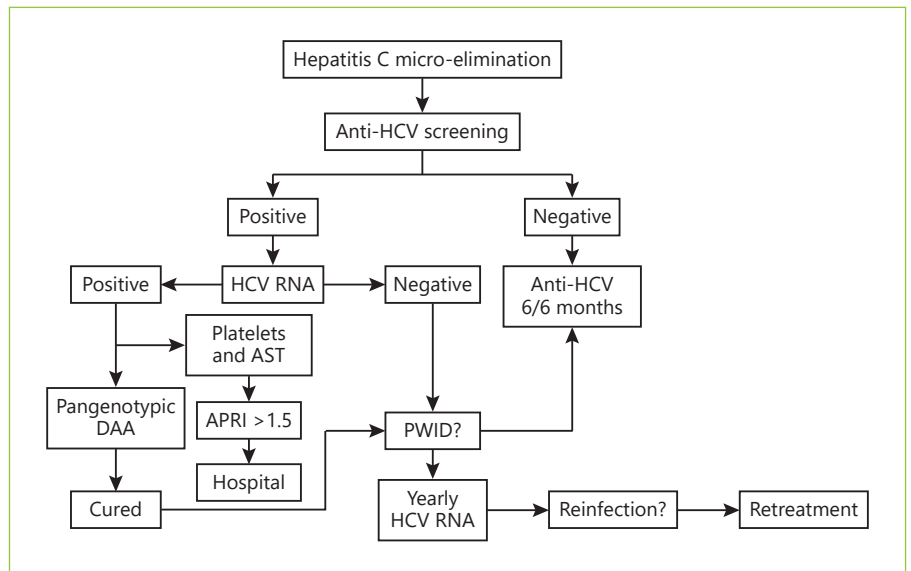


Fig. 2. Proposed algorithm for the diagnosis and treatment of hepatitis C virus (HCV) infection from a micro-elimination point of view. AST, aspartate aminotransferase; DAA, direct-acting antiviral; APRI, AST Platelet Ratio Index.

of vulnerable groups was unfounded, as the cure rate of infection is comparable to that of other populations [35], especially among patients on opioid replacement therapy [36]. In addition, there is a benefit that contributes to the reduction of the risk of transmission and prevalence of infection.

In parallel, pregnant women should be screened for HCV infection and subsequently treated, as well as about 5% of children who become chronic carriers. Injection material (syringes and needles) should be disposable or reused after careful sterilization; ritual practices (circumcision, scarification, tattooing, etc.) controlled [37]; and transfusions of blood or blood products screened appropriately. Some of these risk factors still exist in some developing countries, but they may also occur in migrant communities from regions where HCV infection is highly prevalent (e.g., African countries, India, Pakistan, and Russia) [38].

Therapy as an Elimination Strategy

There are two conflicting strategies for the elimination of hepatitis – micro-elimination and macro-elimination – whose application depends on the epidemiological characteristics of each country. The first is understood as the elimination of infection in specific populations (drug users, prisoners, homeless people, migrants, men who have sex with men, HIV-positive people, etc.) characterized by their high prevalence of infection. There is a consensus among the scientific community that any hepatitis C elimination strategy is doomed to failure unless a pro-

gram of its own is established for these vulnerable populations and treatment for reinfection is included (Fig. 2).

A significant number of countries have been implementing micro-elimination programs both in Europe (Austria, The Netherlands, Spain, etc.) and in other parts of the world (Australia) with remarkable success [39]. In 2016, this effort was still less than desirable as the rate of patients treated was lower than the number of new infections in about half of the countries [32].

To be effective as a method of eliminating hepatitis C, micro-elimination will need to be comprehensive, that is, encompassing the different subpopulations. However, in order to effectively eliminate hepatitis C, micro-elimination will also need to be complemented by screening for infection in the general population (macro-elimination). Some countries (e.g., Egypt, Georgia, and Iceland) with a high prevalence of hepatitis C have decided to implement a universal screening program [29], while in France, perhaps the country with the highest rate of patients diagnosed and treated, universal screening is the most effective strategy and is cost-effective when treatment is initiated regardless of fibrosis stage [9]. In the USA, HCV testing is recommended for individuals born between 1945 and 1965, where the prevalence of infection is 3.25%, and about 50% of all infections [40]. In Portugal, without a plausible explanation, most of the patients diagnosed and treated are in the age range from their 40s to their 60s, and this is eventually related to some specific social and cultural features of the country [10].

There are many impediments that still hinder the access to diagnosis and treatment. Overcoming the barriers listed in Table 1 is fundamental to establish a strategy for effectively eliminating hepatitis C [41, 42], which could simply be summarized in the following three-fold strategy: prevention, testing and treatment. To promote the diagnosis of infected individuals; to provide health facilities and mobile units with conditions to screen and treat vulnerable populations, overcoming the aversion of PWID to healthcare; to facilitate the investigation of viremia by resorting to a rapid test; to simplify clinical procedures and involve primary care physicians in the respon-

sibility of screening and possibly treating; and to reduce the bureaucracy in the access to and dispensing of medication, taking advantage of assisted treatment with opioid replacement therapy, are some of the measures that we consider essential. But these are not enough: it is necessary to establish an elimination plan with allocation of resources and an appropriate national register.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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