Strategy for the elimination of hepatitis C in Cantabria

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Received: 08/04/2020 · Accepted: 12/04/2020
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BACKGROUND

The hepatitis C virus (HCV) is one of the leading causes of liver-related morbidity and mortality worldwide, affecting more than 70 million people (1,2). Approximately, between 55 % and 85 % of infected people will develop chronic HCV infection and between 15 % and 30 % of this group will develop liver cirrhosis and associated complications in the following 20-30 years. In our country, the seroprevalence of anti-HCV ranges from 0.8 to 1.2 % of adult population, while 0.2 % to 0.4 % show active HCV infection (3,4). In recent years, with the appearance of direct-acting antiviral agents (DAAs), which achieve cure rates of over 95 % (5-7), the elimination of HCV is a real possibility. In fact, in 2016 the World Health Organization (WHO) established a global strategy with the goal of achieving its elimination by 2030 (8). This strategy defines elimination as an 80 % reduction in new HCV infection and a 65 % reduction in HCV mortality. In the particular case of Spain, the National Strategic Plan for tackling Hepatitis C infection (PEAHC) has established different lines of action against hepatitis C (9). As a result of the implementation of this program by the Government of Cantabria, since May 2015, almost all known hepatitis C patients from our autonomous community have been treated with DAAs, besides those previously treated with regimens based on interferon. Although a considerable part of the patients has already been treated, the existence of subjects who know the diagnosis of the infection but have not undergone treatment or are unaware of being infected with HCV is rather frequent (10). Multiple reasons exist, including belonging to vulnerable social and at risk of exclusion groups, such as those subject to custodial and non-custodial sentences or intravenous drug users (IDU), and those who have access difficulties (immigrants). In addition, fear or social stigmatization and lack of knowledge of the risk factors for acquiring this infection are other reasons that explain the absence of diagnosis and treatment in some patients, particularly, in the age groups between 40 and 69. This group, which escapes the system and therefore does not benefit from current therapies, leads to diagnostic burnout (10), which is the impossibility of treating current infections due to a lack or difficulty in diagnosing prevalent cases or incidents. If we consider treatment as profitable in this age range, the search for untreated and/or undiagnosed patients seems to be a desirable goal for health systems.

Considering this background, a plan for the elimination of HCV has been designed in our autonomous community. Its main objective is the elimination of hepatitis C in Cantabria in the 2019-2021 period, understanding by elimination the diagnosis and treatment of 90 % of hepatitis C cases. As secondary objectives, we aim to: a) know the burden of C virus in the different primary sources of infection; b) achieve the joining of disadvantaged groups to health services; c) decrease the prevalence of severe liver disease (cirrhosis and hepatocellular carcinoma) secondary to hepatitis C; and d) obtain health results for the shaping of medical knowledge and planning and organizing of future sanitary actions.

MACRO-ELIMINATION AND MICRO-ELIMINATION

The strategy for the elimination of hepatitis C in Cantabria is based on the active search for cases and the immediate treatment of infections detected with DAAs. This strategy

Author’s contribution: Javier Crespo and Ana Tejerina Puente have contributed equally in the manuscript.

DOI: 10.17235/reed.2020.7108/2020
is focused in two different groups (macro-elimination and micro-elimination), depending on whether it is directed at a population age group or the primary sources of infection. Therefore, the target populations will be (Fig 1):

1. In the macro-elimination strategy, the population between 40 and 69. Cases will be systematically searched in primary care consultations, in which about 75 % of the viremic patients not detected so far are found, according to previous studies (3,11).

2. In the micro-elimination strategy, the entire population belonging to a risk group or primary focus of hepatitis C infection. Micro-elimination will be implemented, at the same time, in the vast majority of the primary focal points. These focus include, among others, the following: patients with alcohol user disorder, men who have sex with men (MSM) and have risky practices, immigrants from countries with high prevalence of HCV infection, pregnant women with risky practices or belonging to a primary focus, patients coinfected with human immunodeficiency virus (HIV), patients with advanced liver disease (regardless of the primary etiology of the liver disease), hemophiliacs, patients in hemodialysis programs (active or previous) and/or undergoing a solid or hematological organ transplant, patients with severe chronic mental illness (whether institutionalized or not), subjects in harm reduction programs (substitution treatment with methadone or buprenorphine/naloxone), injecting drug users (active or prior), subjects with group sex and chemsex practices, individuals sentenced to custodial and non-custodial penalties and those living with an HCV-infected person.

The simultaneous implementation of both, macro-elimination and micro-elimination strategies represents, to our knowledge, the first structured experience worldwide that addresses the elimination of HCV in the population of a general community. This program will generate first-rate evidence that can be shared in other regions, both Spanish and foreign, which will allow them to propose their own elimination programs.

**IMPLEMENTATION OF MACRO-ELIMINATION**

The participation of primary care is key in the development of this strategy, especially in the macro-elimination
process. As it has been previously pointed out, this will focus on the systematic search of cases in primary care consultations, in the age group of 40 to 69. That is to say, it is an opportunistic screening, which will be carried out when the patient comes to the consultations of the doctor and/or the primary care nurse. According to our own data and those of the Health Department of the Government of Cantabria, more than 85% of subjects between the age of 40 to 70, at least, once a year to visit the doctor and/or primary care nurse.

The macro-elimination program will be developed with a time horizon of three years, structuring the search for the population as follows (Fig 2): a) year 2019: detection of patients between 50 to 59 years old; b) year 2020: detection of patients between 60 to 69 years old; and c) year 2021: detection of patients between 40 to 59 years old. This schedule has been made taking into account the prevalence of HCV infection in our region. Several studies have shown that population screening associated with treatment is cost-effective in different age ranges and in the general adult population (3,12,13). This has led several scientific societies in our country (Spanish Association for the Study of the Liver [AEEH], Spanish Society of Gastroenterology [SEPD] and the Alliance for Viral Hepatitis Elimination in Spain [AEHVE]) to recommend the establishment of population screening strategies adjusted to the characteristics of the assisted population (14).

The Cantabria Health Service has designed a specific protocol for this healthcare process, which has been included within the personal plans in the electronic medical record of primary care for all patients whose age is among those indicated above. In addition, this protocol will be activated annually for some risk factors for which there is a specific code (alcohol use disorder, drug addiction, hemophilia, some sexually transmitted diseases, etc.).

Neither patients without risk factors with a negative determination made in the previous five years nor those with a previous diagnosis of hepatitis C need to carry out an anti-HCV determination.

**MICRO-ELIMINATION AND DIFFERENTIAL CARE OF VULNERABLE AND/OR HIGH PREVALENCE POPULATIONS OF HCV INFECTION**

The micro-elimination strategy has shown to be effective in other diseases such as HIV infection or, previously, polio. The micro-elimination focuses on the active search for cases in different primary focus with a high prevalence of hepatitis C in the adult population (over 18 years of age). These focuses include, among others, the following:

- History of blood transfusion or hemoderivatives prior to 1992.
- History of surgery, invasive procedures or dental interventions before the use of single-use material.
- People who have undergone procedures with different types of sharp material without adequate security.
- MSM and those with risk practices.
- Subjects with group sex and chemsex practices.
- Patients with alcohol use disorder.
- Homeless people (15).
- Immigrants from countries with a high prevalence of HCV infection.
- Pregnant women with risky practices or belonging to a primary focus (16-18).
- Patients coinfected with HIV and/or HBV (hepatitis B virus).
- Patients with sexually transmitted infections.
- Acute or chronic hypertransaminasemia, provided that the antibodies against HCV had not been determined before.
- Patients with chronic hepatic disease, regardless of the primary etiology of the hepatic disease.
- Hemophilic patients.
- Patients in (active or previous) hemodialysis programs.
- Patients undergoing a solid organ (heart, liver, pancreas, lung, kidney) or a non-solid organ transplant.
- Patients with severe chronic mental illness, whether institutionalized or not.
- Subjects in harm reduction programs (substitution treatment with methadone or buprenorphine/naloxone).
- Injecting drug users (active or prior) and/or those who use inhaled drugs.
- Subjects sentenced to custodial and non-custodial penalties.
- People living with an HCV infected person and sexual partners of infected people (19).

In our community, there are some pioneering programs such as Jailfree (20) or Honest (21) that systematically test (and treat) HCV infection in prison inmates or in those subject to a non-custodial sentence. Similarly, and to facilitate diagnosis for elimination, several community initiatives are facilitating access to diagnosis (22), bringing diagnostic techniques closer to the patient, such as dry blood spot tests (DBST) or diagnostic methods at the point of patient care (23,24). This decentralized diagnosis is integrated into the usual circuits. All diagnoses of active infection by positive detection of viral RNA are included in a weekly electronic alert that is evaluated by the Hepatology Unit of the Digestive Diseases Department.

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Fig. 2. *Macro-elimination pillar. The implementation of this part of the strategy will be carried out gradually by age group.*
GENERAL MODEL OF INTERVENTION: DIAGNOSIS, TREATMENT AND FOLLOW-UP (Figs. 3 and 4)

After identifying the subjects that are the object of the program, their primary care physician in the macro-elimination program or both levels of care in micro-elimination will invite them to participate. Once informed, the subjects who agree to participate will undergo a reflex testing of hepatitis C (25), that is to say, in those who are positive in serology, the Microbiology Laboratory will automatically perform the viral load determination by PCR, without the need of a new blood draw. The same process will apply in the few subjects with an indeterminate result in serology. Subjects with a negative result will be informed by the doctor who invited them to participate in the program. In the absence of risk factors, test repeat will not be required. In the event that the person persists with a situation that increases the risk of HCV infection, their doctor will explain the need for regular annual monitoring (6).

As previously mentioned, patients with active infection will be identified by the Hepatology Unit through an electronic alert. These patients will be automatically appointed (the patient does not need to visit the doctor who requested the new referral petition) with the Digestive Disease Department of his reference hospital, where the study will be completed in a maximum period of three weeks. This short period of time is possible thanks to a reflex testing (reflex test) and the implementation of an automated alert system that reports positive cases every week and largely prevents the loss of patients in the stream of care for these ones (26). In the first visit, the disease will be diagnosed in reflex testing. The disease will be characterized in terms of severity by carrying out a test in which a sample will be extracted for a potential phylogenetic analysis of the virus (to subsequently determine possible reinfections). In addition, a transition elastography to determine the degree of liver fibrosis and an abdominal ultrasound will be performed. At the end of the consultation, the corresponding treatment will be prescribed, which will be dispensed in the Pharmacy Service. During this first consultation, a report will be issued detailing all the relevant data on the patient’s history, treatment and follow-up.

FOLLOW-UP AND DETECTING REINFECTIONS

Although the follow-up of the treated patients will be individualized, the program foresees a homogeneous follow-up after the start of the treatment that involves:

1. A test 12 weeks after the end of the treatment, in which the existence of a sustained virological response (SVR) is determined; this response will probably be obtained in more than 95 % of cases. This will be the only follow-up consultation for patients with non-advanced fibrosis who have SVR. Patients with advanced fibrosis and SVR will

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Fig. 3. Macro-elimination healthcare circuit. Workflow for the population screening from the initial test, evaluation of the disease, prescription of treatment and follow-up recommendations.
be followed in the Digestive Diseases Department to complete the observation programs for the development of esophageal varices and screening for hepatocellular carcinoma according to standard clinical practice.

2. Patients who do not present an SVR will be offered rescue treatment (after studying resistance if adherence has been correct) and a subsequent evaluation according to standard clinical practice.

DISSEMINATION, COMMUNICATION AND TRAINING

Before the effective start of the hepatitis C elimination plan in Cantabria, a dissemination, communication and training program was developed. It included all the doctors and nurses from the Cantabria Health Service.

1. Communication to professionals. After the approval of the final version of this elimination plan, it was disseminated to all the professionals involved. Furthermore, an informative scientific conference was held for all the professionals involved in which the program was exhibited and the different circuits and algorithms for action were presented.

2. Training of the professionals involved. During the months of April and May 2019, a training program was held for the professionals involved in conducting this program, which entailed one or more visits to health centers, in-hospital sessions, visits to holding facilities and others for special populations targeted by the program.

3. Public dissemination of the health problem. During the first half of March 2019, an institutional campaign to publicize hepatitis C as a health problem was carried out and the strategy for the elimination of hepatitis C was presented at a public event at the Hospital Universitario Marqués de Valdecilla.

PROGRAM EVALUATION

In order to evaluate results periodically, which in turn helps correct deficiencies, the following series of indicators have been defined for the program itself:

- Percentage of centers, services and health professionals and other professionals involved in the care of these patients who participate in the HCV elimination program.
- Target population of each program, detection rate, systematic detection and evaluation of the prevalence of HCV infection in the study population.
- Degree of compliance: a) diagnosis of the infection in a single step; b) diagnosis of the disease in a single step;
c) treatment established in the first consultation; and e) time of diagnosis and establishment of treatment.

- Data regarding infection, disease and treatment: a) percentage of patients with previous known/unknown infection; b) percentage of patients with mild/advanced disease; c) existence or not of extrahepatic disease; d) coinfection or not with HIV and/or HBV; e) form of presentation of the disease: early or late; f) existence and type, where appropriate, of decompensations of the liver disease; g) development or not of hepatocellular carcinoma; h) type of treatment; and i) reinfections.

This monitoring of the program operation and results is under continuous evaluation and will be adapted to the recommendations that are published (27) with the ultimate goal of being able to demonstrate the elimination of hepatitis C in our region.

**WORKING GROUP IN THE STRATEGY DESIGN FOR THE ELIMINATION OF HEPATITIS C IN CANTABRIA**


**REFERENCES**


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