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Lucía Seoane Blanco, Javier Soto Sánchez , Gema Sierra Dorado , Leire Parapar Álvarez , Manuel Crespo Sánchez , Luis Sánchez Domínguez , Juan de la Vega Fernández

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Active search for hepatitis C patients in Primary Care.

AUTHORS:

Lucía Seoane Blanco ¹, Javier Soto Sánchez ¹, Gema Sierra Dorado ², Leire Parapar Álvarez ¹, Manuel Crespo Sánchez ¹, Luis Sánchez Domínguez ¹, Juan de la Vega Fernández ¹.

1. Gastroenterology Department. Hospital Universitario San Agustín. Avilés, Asturias. Spain.
2. Microbiology Department, Hospital Universitario San Agustín. Avilés, Asturias. Spain.

Corresponding author: Lucía Seoane Blanco. Mail: lucvar24@gmail.com

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CONFLICT OF INTEREST

Juan de la Vega Fernández: consultant and speaker of Gilead and Abbvie. Other authors declare no conflict of interest.

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ABSTRACT

Introduction: Undiagnosed hepatitis C virus (HCV) active infections pose a problem to achieve the WHO (World Health Organization) hepatitis C elimination goal in 2030. One of the possible strategies to identify these patients is the active search for patients in Primary Care (PC).

Methods: We reviewed patient's medical record in PC with a "hepatitis C" open case in the last five years. We included those with uncompleted diagnostic study – due to the absence of active infection confirmation –, or those who did not start or finish treatment. A blood analysis was recommended to prove the existence of the active infection. The one-step diagnosis (OSD) was implemented to assess the viremia in all patients with a new serologic diagnosis.

Results: Of 253 cases with a "hepatitis C" open case in their medical records, 24.1% (61) did not finished the diagnostic study or did not follow the treatment. Four of them were not suitable candidates to finish the study. Of the other 57, 92.9% accepted diagnostic test. Active infections were confirmed in 40 patients (75.4%) and the treatment was completed in all of them.

Conclusions: Active search for patients with hepatitis C in PC together with the OSD are effective measures to detect hidden infections and to increase the number of treatments, contributing to the elimination of hepatitis C.

INTRODUCTION

In Spain, a high number of patients with hepatitis C virus (HCV) infection has already been treated, mainly, after the development of a national strategic plan ("Plan Estratégico para el Abordaje de la Hepatitis C, PEAHC") in 2015 (1). However, there is still a significant percentage of people (2-4) who ignore they are infected, with most of them belonging to risk groups. The diagnostic study was not finished in some asymptomatic patients or the treatment was not carried out in the past, before the development of direct-acting antivirals (DAA), due to patient's refusal or intolerance. In addition, other patients had been treated, but they were lost to follow-up.

In order to achieve the WHO (World Health Organization) hepatitis C elimination goal in 2030 (5), it is necessary to carry out strategies to identify hidden infected patients. Different measures have been proposed, such as mass population screening or selected screening according to age cohorts (6) for early detection of hepatitis C in asymptomatic

patients, micro-elimination programs in vulnerable groups (prisoners, people who inject drugs, etc) or the active search for patients in Primary Care (PC). Another possibility is the implementation of an one-step diagnosis (OSD) of the HCV infection, among other options.

Taking into account these facts, we designed a study aiming to treat the possible unknown active infections with current therapies. This involved an active search for patients in our health area who previously had not completed the diagnostic study or had not initiated or completed therapy.

MATERIALS AND METHODS

All patients from the Health Area III of the Principality of Asturias (total population of 145.487 inhabitants) who have an open case of “hepatitis C” in their medical record of PC in the last five years were identified through an ICPC (International Classification of Primary Care) code. The search for patients with this code was performed by the Information and Technology Department of our hospital. Later, we checked the electronic medical records to identify suspect cases, due to personal risk history such as drug use, but unconfirmed (positive serology, without viremia analysis), diagnosed but untreated, and treated without confirmed cure. Data about demographic variables (sex, age, health center), infection route and HCV infection (existence of serology and viremia analysis or if patients had received treatment previously) were collected.

With permission of the Board of Health Care and Public Health of our hospital, general practitioners with suitable candidates to complete the hepatitis C study were informed through the health care center coordinator. Patients were contacted to participate with a new blood sample including serology or viral load analysis.

Together with Department of Microbiology, an OSD was set up to assess the viremia in the same blood sample in all patients with a new serological diagnostic. Those with negative anti-HCV or with a combination of positive anti-HCV but negative viremia were excluded. They were informed by telephone. In contrast, patients with positive anti-HCV and

positive viremia were recommended to go to the Gastroenterology consultation. If they did not attend, they were contacted again for another appointment from our consultation.

On the Gastroenterology consultation, an ultrasound examination was carried out to assess a possible hepatopathy and to rule out focal liver lesions. Besides, a transient elastography was fulfilled to evaluate the fibrosis stage. If a transient elastography could not be carried out, biochemical diagnostic tests – APRI and FIB-4 – were performed. Later, and according to the patient's wishes to be treated, a treatment with pan-genotypic DAA was prescribed after explaining the diagnosis.

A blood analysis was performed twelve weeks after finishing the treatment to assess sustained virological response (SVR). Eventually, the participation and the prescribed treatments were evaluated between November 2018 and February 2020. In this study, an intention to treat analysis of outcomes was performed.

This prospective and descriptive study was designed according to the principles of the Declaration of Helsinki and was approved by the Research Ethics Committee of the Principality of Asturias. The access to the patient's medical record and the information analysis were carried out only by the researchers involved in this project. This information was collected confidentially in an anonymous data base. All patients were appropriately informed and approved their participation with an informed consent. The participation in this project did not need further invasive tests additional to the ones already performed in the routine clinical practice with these types of patients.

RESULTS

A total of 253 patients with the code "hepatitis C" in the PC medical record were found (Figure 1). From them, 192 patients were dismissed due to several reasons: 164 were diagnosed of hepatitis C and treated, achieving SVR in 99.4% of the cases (39.6% continue the follow-up due to advanced fibrosis); 22 cases had negative viral load, suggesting they overcame the infection; in two cases, they were not correctly identified as they were

never anti-HCV positive; finally, two people died and two other people moved to another health area.

Of the remaining 61 patients (24.1%), four were not suitable candidates to continue the study due to their advanced dementia and multiple associated comorbidities, such as spastic paraplegia and advanced kidney and heart failures. Practitioners informed the other 57 people that a blood analysis was necessary. They should be referred to the Gastroenterology specialist if they had an active infection. 15 people (26,3%) did not attend to the first appointment, hence, a second call was needed from the Gastroenterology office.

Of 57 selected patients, four rejected their participation due to a number of reasons, such as being asymptomatic, refusing a treatment or having other active comorbidities in treatment. The remaining 53 accepted to perform a blood analysis to confirm or rule out the active HCV infection (Table 1).

- 60.4% (n=32) of patients had suspicion of HCV infection, but unfinished diagnostic study (n=12) or they had been already diagnosed with HCV infection (n=20), but untreated. These 32 patients performed a new blood analysis and all of them had active infection.

These patients had attended their health center due to another reason in the past. At that moment, general practitioner had registered an open case of “hepatitis C” in their medical record to rule out hepatitis C (suspicion of HCV infection because of risk factors such as drugs consumption) with a blood diagnostic test. Nevertheless, diagnostic tests to confirm or reject the possible infection were not eventually performed, in many cases due to poor adherence or lack of awareness. Other cases had shown positive serology, but viremia was not analyzed, before the implementation of the OSD, hence active infection had not been confirmed.

- 24.5% of patients had been already treated previously; most of them with peginterferon and ribavirin. However, cure was not checked up due to loss of follow-up. 38.5% of this group had SVR, while 61.5% (n=8) presented active infection.

- 15.1% of patients showed negative viremia, suggesting a spontaneously resolved HCV infection.

Based on these results, we can point out a participation of 92.9% (53 out of 57 patients included in the study), detecting active infection in 40 people (75.4%).

Among patients with HCV active infection (Table 2), 72.5% were male, with a mean age of 55 years (range 36-87) and the different putative mechanisms of infection were the following: 20 (50%) were current or past parenteral drug users, 4 (10%) acknowledged having received blood transfusions before 1991, 3 (7.5%) of them had been operated in the past and one (2.5%) got an amateur tattoo. In twelve cases (30%), the origin of the infection was unknown. Regarding the determination of the liver fibrosis stage, an advanced stage (F3-F4) was detected for 42.5% of patients with an active infection.

The 40 patients were treated with glecaprevir/pibrentasvir (47.5%), sofosbuvir/velpatasvir (45%), sofosbuvir/velpatasvir/voxilaprevir (5%) and sofosbuvir/ ledipasvir (2.5%). 35 out of 40 treated patients (87.5%) were confirmed to have SVR. The post-treatment analysis of one patient (2.5%) is pending; while four others (10%) did not perform a blood analysis after week 12 post-treatment. This was regarded as a non-virological failure. However, all of them picked the medication up in the Hospital Pharmacy and completed the treatment.

DISCUSSION

In this study, we evaluated the results from the implementation of a micro-elimination strategy. This strategy consists in the active search for patients in PC with an incomplete diagnostic for hepatitis C (positive serology for HCV, no viremia analysis to confirm an active infection) or patients with incomplete treatment. The aim was to treat the patients with unknown active infections.

Different scientific societies recommend starting up HCV infection micro-elimination projects. They consist in dividing the elimination global strategy, focusing their programs on primary care spots of the infection (3).

In our study, we followed such a strategy identifying patients within the PC structure. In this context, many unstudied viremic patients can be located (3-4). Moreover, there is an advantage of greater contact and knowledge of the patients. It facilitates the identification of patients with risk factors, such as parenteral drug use, which represents 50% of the patients included in this study. However, the origin of infection was unknown in 30% of cases, thus favoring the absence of diagnostic suspicion and increasing the percentage of hidden infections.

24.1% of patients with a “hepatitis C” code in the PC medical record did not complete the diagnostic study or receive the treatment. This significant and alarming percentage might be favored by various causes. Some cases with suspected infection (due to personal risk history) were detected. However, active infection was not confirmed because these patients did not attend to perform a load viral analysis – before the OSD implementation – due to several reasons, such as lack of awareness, absence of symptoms, belonging to vulnerable social groups, poor adherence, fear of the social stigmatization, etc. Some patients were referred to the Gastroenterology office. Nevertheless, the delays in hospital care, the lag in finishing the diagnostic study or treatment access might have hindered the beginning of treatments. In other cases, therapy was not completed or follow-up was lost. A recent study (7) observed that patients not referred to the Hepatology office or lost in the follow-up had a higher rate of drug consumption, methadone therapy, history of psychiatric pathology or other comorbidities such as COPD, diabetes, hypertension. They could also be prisoners or institutionalized patients, some patients had changed their living address or showed normal values for transaminases. As in our study, the authors showed that more than 20% of PC patients with a positive anti-HCV serology had not been referred to the specialist and 22% had not finished the diagnostic study due to not attending to the specialised consultation.

Candidate patients were contacted and informed to be included in the study with a high participation of 92.9%. It was key to transmit the importance of the diagnostic confirmation, inform them about the new therapeutic possibilities, as well as simplifying the diagnostic process, and creating hospital high-resolution consultations (3-4).

The development of an active intervention allows the identification of a remarkable number of HCV infections (8). As we show in our study, 75.4% of the participants had an active infection. Of them, 42.5% were diagnosed with an advanced fibrosis stage. Treatment with DAA was initiated in all screened patients who had an active infection, obtaining 87.5% SVR by intention to treat analysis. Currently, SVR result is pending for another patient. 10% of the patients did not perform the post-treatment analysis, although they did the full treatment. The results show that this strategy is valid to improve the search for patients with HCV hidden infections.

A recent study (9) showed that the search for lost patients is probably one of the most profitable strategies. It is due to the percentage of PC patients with unfinished diagnostic studies or treatments, as well as the ease of their detection via access to hospital or PC databases. In addition, it should be noted that there is enough ethical-legal endorsement to detect and contact with these patients, considering the individual benefit and with respect to public health.

In addition, to increase the detection of hidden infection, it would be necessary to consider the development of other strategies like the implementation of population screening programs in different age groups and in all the adult population who attends PC, as established in the Spanish community of Cantabria (6). Although these programs are more expensive than the specific risk screening, they would allow the early diagnosis and treatment of hepatitis C. It would also stop transmission and the long-term hepatopathy complications. With these results, this measure would become cost-effective, as stated in other documents (10-11).

Another relevant measure is the OSD implementation. It means a greater access to treatment without unnecessary delays or follow-up losses, as seen in some regions after its implementation (12-14). Besides, it also simplifies the final hepatitis C diagnostic, being a cost-saving measure compared to the traditional procedure (15).

To avoid losing the patients with positive anti-HVC or positive viremia, artificial intelligence might be applied in some health registrations, as done in other autonomous communities (8).

The limitations of this study are its small size and the participation of patients from only one health area. The results found may not be relevant to other population areas with different characteristics. In addition, it must be highlighted that some patients rejected to take part in the study and 10% of them did not come back to check if SVR was achieved after finishing the treatment, this was regarded as a non-virological failure. Thus, it is highly important to detect predictive factors of loss of follow-up (7) and implement measures to link these patients to the health system (16).

In conclusion, the active search for patients with hepatitis C as well as the OSD implementation are effective strategies to detect hidden infections and increase the number of potential treatments, to achieve the WHO goal of eliminating the hepatitis C (5). However, it is necessary to improve the bonds between the patient and the health system to avoid their loss during the diagnostic study or the therapy.

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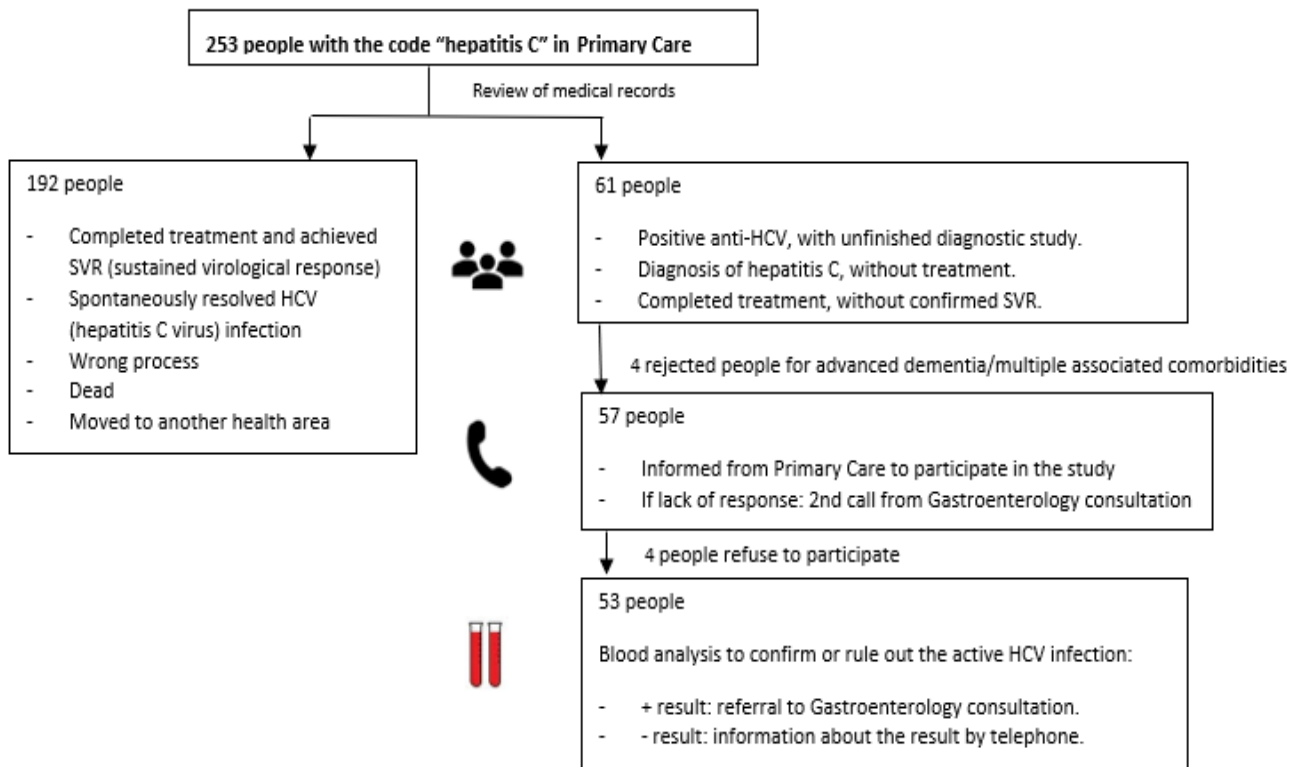


Figure 1. Flowchart.

Table 1: Classification of people with the code “hepatitis C” in Primary Care medical record.

People with the code “hepatitis C” in Primary Care: 253	
Dismissed people	192 (75,9%)
Completed treatment and achieved SVR	164
Spontaneously resolved HCV infection	22
Wrong process	2
Dead	2
Moved to another health area	2
People with unfinished diagnostic study, untreated or without SVR	61 (24,1%)
Rejected (advanced dementia/multiple associated comorbidities)	4
Candidates to continue the study	57
➤ People who refuse to participate	4
➤ People who accept to participate	53 (92,9%)
• Suspicion of infection or confirmed diagnosis, without treatment	32 (60,4%)
• Completed treatment, not confirmed SVR	13 (24,5%)
• Spontaneously resolved HCV infection	8 (15,1%)

Table 2: Characteristics of people with active infection.

Characteristics of people with active infection.	
Total	40 (100%)
Sex	
Male	29 (72,5%)
Female	11 (27,5%)
Mean age	55 (36-87)
Putative mechanisms of infection	
Parenteral drug users	20 (50%)
Unknown	12 (30%)
Previous transfusions	4 (10%)
Surgical intervention	3 (7,5%)
Amateur tattoo	1 (2,5%)
Genotype	
1a	6 (15%)
1b	10(25%)
3	12 (30%)
4	1 (2,5)
Mixed	2 (5%)
Unknown	9 (22,5%)
Fibrosis stage	
- F0-F1	18 (45%)
- F2	5 (12,5%)
- F3	11 (27,5%)
- F4	6 (15%)
People who receive treatment	40 (100%)
Treatment	
GLE/PIB	19 (47,5%)
SOF/VEL	18 (45%)
SOF/VEL/VOX	2 (5%)
SOF/LED	1 (2,5%)
Viral load week 12 post-treatment (SVR)	
Confirmed	35 (87,5%)
Pending	1 (2,5%)