Enferm Infecc Microbiol Clin. 2019;37(4):219–221

Enfermedades Infecciosas y Microbiología Clínica

www.elsevier.es/eimc

Editorial

Hepatitis C virus infection in Spain: Challenges in the track to elimination

Infección por el virus de la hepatitis C en España: desafíos en el camino hacia la eliminación

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Hepatitis C virus (HCV) infection is still a major public health issue in Spain. Until the first half of the present decade, hepatitis C was the first cause of end-stage liver disease and the main reason for liver transplant in Spain.[1] After the introduction of direct acting antiviral therapy (DAA), the morbidity and mortality associated with HCV infection have dramatically declined. However, this disorder is far from residual. Thus, the current anti-HCV prevalence among the general population in our country found in a recent national seroprevalence survey was 0.8%, with 0.17% subjects who tested positive for plasma HCV-RNA.[2] Importantly, no case in subjects younger than 20 was identified. Accordingly, the estimated overall Spanish population infected with HCV is about 70,000–80,000 patients at the end of 2018.

Genotype distribution in Spain is the reflection of changes in the routes of HCV transmission over the years. In patients older than sixty, HCV infection was mainly acquired through blood transfusions and unsafe medical procedures, and in this subset genotype 1b is largely the most common one. As the safety of medical care improved, and with the increase of injecting drug use in the last quarter of the twentieth century, drug use becomes the uppermost way of HCV spreading in our area. Consequently, younger patients got HCV infection mainly through the use of injecting drugs with shared equipment. In this population, the frequency of genotype 1a, 3 and 4, which are linked to drug use, is greater that in older patients. In this issue, Navarro et al. compare the distribution of HCV genotypes in Galicia between 2000 and 2015.[3] The pattern is similar to the rest of Spain and translates the above-mentioned waves in the introduction of genotypes in our country. Although genotype 1b is still the most frequent one, there has been a fall in its prevalence and a significant increase of genotype 2, 3 and 4. Furthermore, genotypes 1b and 2 are more frequently associated with female sex and older ages, whereas 1a, 3, and 4 are linked with male sex and younger ages, because drug users are more commonly men and younger than patients infected through unsafe medical procedures.

With the advent of direct-acting antivirals (DAA), the elimination of HCV has been perceived as a feasible goal. In 2016, the World Health Organization (WHO) proposed its first global strategy toward ending viral hepatitis.[4] The strategy called for eliminating HCV as a major public health threat by 2030, reducing its incidence by 90% and promoting a 65% reduction in HCV mortality. Because of the complexity of an effective global intervention, the concept of micro-elimination has been proposed: it consists in splitting the overall objective into smaller goals for individual population segments, for which treatment and prevention are easier to implement.[5] Micro-elimination may be successfully achieved in specific sub-populations, in which it is workable to adapt diagnosis, treatment settings and surveillance to its particular circumstances. These populations would differ depending on the epidemiology and health context of the country. In Spain people who use drugs, prison inmates, HIV/HCV-coinfected subjects and migrants are proper candidates to be established as micro-elimination target groups.

The main route of new and existing HCV infections in high-income countries is the use of drugs, either injected or inhaled, with unsterile devices. HCV incidence is high among this group, which is probably driven by a limited or no access to care. This situation may generate potential pockets of infection, and this is why HCV micro-elimination in drug-users must be a priority goal. Besides, risk behaviors, especially drug use, are common in prison inmates, where anti-HCV prevalence reach 13% in Spain.[6] Closed settings may be the perfect location to easily provide testing and HCV treatment with an 8 or 12-week current DAA regimen, as inmates are readily attainable. Because of HIV and HCV share similar transmission routes, the prevalence of HCV exposure among HIV-infected individuals in Spain reached very high levels, involving 40–70% of patients.[7] HIV/HCV-coinfected individuals receive therapy lifelong and are regularly followed in Infectious Diseases units, being the HCV serostatus usually known. For this reason, these patients are easily available for HCV treatment. Finally, Spain has one of the largest migrant populations in Europe. Migrants and refugees are at a greater risk of being infected with HCV, usually due to an

DOIs of original articles: https://doi.org/10.1016/j.eimc.2018.03.010, https://doi.org/10.1016/j.eimc.2018.05.016, https://doi.org/10.1016/j.eimc.2018.04.002

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https://doi.org/10.1016/j.eimc.2019.01.004

upraised HCV prevalence in their country of origin and to a greater probability of risk exposure during the migration process.[8] In a systematic review and metanalysis conducted by Lazarus et al. and published in this issue,[9] the estimated anti-HCV prevalence among the overall migrant population in our country is comparable to that of Spanish population. When segregating by the origin region, the highest prevalence was found among European [7.1%, 95% CI (2.2–14.2%)] and sub-Saharan African migrants [3.6% (1.5–6.4%)]. Conversely, the figure observed in those from Latin America was 0.9% (0.2–1.8%). Accordingly, the origin of migrants could be used as an indicator to prioritize microelimination strategies. However, microelimination in migrants presents several challenges, such as the absence of a population census and the lack of health data on migrants, as the authors state.

An increasing number of countries are launching HCV elimination or microelimination plans. Based on their specific needs, countries such as Egypt, Iceland, Australia or Georgia[10–13] initiated key activities based upon universal access to HCV treatment. The results are promising with reductions of the overall HCV prevalence and the incidence of new infections. This objective is being achieved very quickly in populations in which all or most HCV-infected patients had been previously diagnosed, as in people who inject drugs (PWID) in Iceland[11] or in HIV/HCV-coinfected men who have sex with men in Switzerland or Netherland[14,15] and more slowly in these settings where the whole target population had not been previously screened, such as in general population in Georgia.[13] The lesson learnt from these programs is that HCV elimination is feasible, but three requirements must be fulfilled: (1) universal access to treatment and maximization of treatment adherence, (2) large-scale population screening, and, (3) implementation of harm reduction programs.[16]

In Spain, universal access to treatment should not be a drawback, because DAA therapy for all HCV-infected patients, irrespective the liver damage, was approved in June 2017. This measure has translated into a reduction in the overall prevalence of active HCV infection and in the incidence of new infections in other countries.[11,14,15] However, there are specific groups in which access to treatment is still limited, in spite of the fact that treatment is reimbursed. This is the case of some PWIDs and migrants. A part of PWID population does not attend centers for opioid substitution therapy (OST), refuse screening or, even after testing positive, they do not attend outpatient clinics to be given DAA. Thus, a recent study has shown that this proportion reaches 31% of patients with active HCV infection.[17] Similarly, some irregular migrants remain outside the health care system, and they will hardly receive therapy against HCV. Besides, good adherence is important to achieve SVR. Thus, PWIDs reach rates of SVR similar to that of general population if they have a minimum adherence, as happened in clinical trials.[18] However, in real-life, when adherence to treatment and follow-up are poorer, the SVR rates by intention to treat markedly decline.[19] In order to improve linkage to care, the consensus of GEHEP-SEIMC and three Spanish societies of addition care[20] recommends peer-driven support, using telemedicine as well as easing inter-level coordination for specialist appointments and treatment follow-up in drug users and prison inmates. Also, to maximize treatment adherence, this consensus propose adherence surveillance by peer support and shared data registration systems. Other strategies aimed at this goal include treatment co-location in addiction treatment facilities and directly observed therapy in these institutions and in jails.

Once universal treatment is available, the overall target population for elimination has to be screened for HCV. HCV screening programs can be addressed to specific groups, such as risk groups, generational cohorts, geographic areas, etc. However, recent studies indicate that universal screening should be considered, as it is a cost-effective strategy to increase diagnosis rates, although it could be more difficult to conduct in the short term.[21] Unfortunately, the Spanish Plan for Hepatitis C has not been updated to undergo a mass screening program yet. In the last months of 2018, some Spanish autonomous regions have started programs aimed to universal HCV screening. It would be desirable that similar plans are launched in the next few months in the remaining Spanish regions.

'One-step' or 'reflex' diagnosis, i.e. testing HCV antibodies and RNA in the same sample, helps identifying all subjects with active infection and avoids loss of patients. In this issue, Crespo et al. analyze the available resources for HCV infection diagnosis within 90 Spanish hospitals.[22] A great proportion of the surveyed hospitals (81%) had technical resources to carry out reflex diagnosis. However only 31% of them did perform it and no more than 44% of the respondents believed that diagnosis should be done in a single blood sample. Some kind of communication strategy was used in 68.9% of the hospitals to notify active infections when diagnosed. According to these data, much can be done regarding to improve the one-step diagnosis of HCV infection and to communicate results to the clinicians in charge of the patients. And, most important, resources for implementing both actions are already available, as this study has proven. Other strategies, as HCV screening in addiction treatment facilities, in primary care institutions or point-of-care facilities may improve the results.

Even with universal screening and treatment, HCV elimination can be hindered if harm reduction programs to prevent HCV transmission are not applied. In fact, patients who achieve SVR may be reinfected if they continue to be engaged in risk practices.[23] Because of this, WHO identify OST, as well needle and syringe programs, as the highest priority of core interventions in PWID. Similarly, men who have sex with men (MSM), another group with a high incidence of reinfections,[23] should use condoms in all intercourses and avoid potentially bleeding sexual practices.[20] At an individual level, other strategies that should be implemented include acknowledging the potential of reinfection, education and counseling regarding HCV transmission and drug use.

In summary, we currently have the opportunity to eliminate in the short-term a major public health problem in Spain, such as HCV infection. We have already taken several important steps in this track, as treatment reimbursement for all HCV infected patients and advances in harm reduction strategies, including an improvement in TSO and in needle/syringe exchanging program access. However, we have still to face a number of challenges in our roadmap. The most important ones are to conduct a mass screening of all potentially infected population and to carry out actions aimed to improve link to care in specific populations that are outside the health care system, mainly some PWIDs and irregular immigrants. If we succeed in implementing these actions, the objective of eliminating HCV infection will become a reality in the first years of the next decade.

Funding

The present investigation has not received specific grants from public sector agencies, commercial sector or non-profit entities.

Conflict of interests

Juan A. Pineda has received research grants from Abbvie, Janssen, Gilead, MSD y ViiV, talk honoraria from Abbvie, Janssen, Gilead, MSD and ViiV, financial support to attend educational activities from Janssen and Gilead and has been an advisor of Abbvie, Janssen, Gilead and MSD. The remaining author reports no conflict of interest.

References

1. Bruguera M, Forns X. Hepatitis C in Spain. Med Clin (Barc). 2006;127:113–7.
2. La Moncloa [Internet]. Madrid: Gobierno de España; 2018. Available from: http://www.lamoncloa.gob.es/serviciosdeprensa/notasprensa/sanidad/Paginas/2018/301018-hepatitis.aspx [updated 30.10.18; cited 28.11.18].
3. Navarro-de la Cruz D, Pérez-Castro S, Trigo-Daporta M, Aguilera-Guirao A. Prevalencia y distribución de los genotipos del virus de la hepatitis C en Galicia durante el periodo 2000-2015. Enferm Infecc Microbiol Clin. 2019;37:256–9.
4. World Health Organization. Global health sector strategy on viral hepatitis, 2016–2021: towards ending viral hepatitis; 2016. Available from: http://apps.who.int/iris/bitstream/handle/10665/246177/WHO-HIV-2016.06-eng.pdf [cited 14.11.18].
5. Lazarus JV, Wiktor S, Colombo M, Thursz M. Micro-elimination – a path to global elimination of hepatitis C. J Hepatol. 2018;67:665–6.
6. Cuadrado A, Llerena S, Cobo C, Pallás JR, Mateo M, Cabezas J, et al. Microenvironment eradication of hepatitis C: a novel treatment paradigm. Am J Gastroenterol. 2018;113:1639–48.
7. Cifuentes C, Mira JA, Vargas J, Neukam K, Escassi C, García-Rey S, et al. Prevalencia de los marcadores de infección de los virus de las hepatitis en pacientes portadores del VIH en el sur de España. Enferm Infecc Microbiol Clin. 2012;30:452–7.
8. Lazarus J, Safreed-Harmon K, Thursz M, Dillon J, El-Sayed M, Elsharkawy A, et al. The micro-elimination approach to eliminating hepatitis C: strategic and operational considerations. Semin Liver Dis. 2018;38:181–92.
9. Lazarus J, Bromberg D, del Amo J, Norgaard O, García-Samaniego J, Casellas A, et al. Hepatitis C prevalence among the migrant population in Spain: a systematic review and meta-analysis. Enferm Infecc Microbiol Clin. 2019;37:222–30.
10. Omran D, Alboraie M, Zayed RA, Wifi M-N, Naguib M, Eltabbakh M, et al. Towards hepatitis C virus elimination: Egyptian experience, achievements and limitations. World J Gastroenterol. 2018;24:4330–40.
11. Tyrfingsson T, Runarsdottir V, Hansdottir I, Bergmann OM, Björnsson ES, Johannsson B, et al. Marked reduction in the prevalence of hepatitis C viremia among people who inject drugs during 2nd year of the Treatment as Prevention (TraP HepC) program in Iceland. J Hepatol. 2018;68:S52.
12. Kwon JA, Dore GJ, Grebely J, Hajarizadeh B, Guy R, Cunningham EB, et al. Australia on track to achieve WHO HCV elimination targets following rapid initial DAA treatment uptake: a modeling study. J Viral Hepat. 2018, http://dx.doi.org/10.1111/jvh.13013 [Epub ahead of print].
13. Sergeenko D, Gamkrelidze A, Tsertsvadze T, Kamkamidze G, Metreveli D, Sharvadze L, et al. Progress toward hepatitis C virus elimination through provision of care and treatment services Georgia, 2015–2017. J Hepatol. 2018;68:S171.
14. Braun D, Hampel B, Nguyen H, Flepp M, Stoeckle M, Béguelin C, et al. A treatment as prevention trial to eliminate HCV in HIV+MSM: the Swiss HCVREE Trial. In: CROI. 2018.
15. Boerekamps A, Newsum AM, Smit C, Arends JE, Richter C, Reiss P, et al. High treatment uptake in human immunodeficiency virus/hepatitis C virus-coinfected patients after unrestricted access to direct-acting antivirals in the Netherlands. Clin Infect Dis. 2018;66:1352–9.
16. Ward JW, Hinman AR. What is needed to eliminate hepatitis B virus and hepatitis C virus as global health threats. Gastroenterology. 2018, http://dx.doi.org/10.1053/j.gastro.2018.10.048 [Epub ahead of print].
17. Iglesias M, Macías J, Merchante N, Rincón P, Corma-Gómez A, Sayago C, et al. Barreras para la eliminación de la infección por VHC en usuarios de drogas y otros colectivos con riesgo de exclusión social: Proyecto Hepcare Europe. Enferm Infecc Microbiol Clin. 2018;36 Suppl Espec Cong 2:p25–6.
18. Cunningham EB, Amin J, Feld JJ, Bruneau J, Dalgard O, Powis J, et al. Adherence to sofosbuvir and velpatasvir among people with chronic HCV infection and recent injection drug use: The SIMPLIFY study. Int J Drug Policy. 2018;62:14–23.
19. Macías J, Morano LE, Téllez F, Granados R, Rivero-Juárez A, Palacios R, et al. Response to direct antiviral therapy among ongoing drug users and people receiving opiod substitution therapy in Spain, 2018. J Hepatol. 2019 [in press].
20. Pineda JA, Climent B, García F, García Deltoro M, Granados R, Gómez F, et al. Executive summary: consensus document of GEHEP of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC), along with SOCIDROGALCOHOL, SEPD and SOMAPA on hepatitis C virus infection management in drug users. Enferm Infecc Microbiol Clin. 2018. Available from: https://www.sciencedirect.com/science/article/pii/S0213005X18302660?dgcid=rss_sd_all
21. Deuffic-Burban S, Huneau A, Verleene A, Brouard C, Pillonel J, Le Strat Y, et al. Assessing the cost-effectiveness of hepatitis C screening strategies in France. J Hepatol. 2018;69:785–92.
22. Crespo J, Lázaro de Mercado P, Blasco Bravo AJ, Guirao A, García-Samaniego Rey J, Eiros Bouza JM, et al. El diagnóstico de la infección por el virus de la hepatitis C en España: una oportunidad para mejorar. Enferm Infecc Microbiol Clin. 2019;37:231–38.
23. Midgard H, Weir A, Palmateer N, Lo Re V, Pineda JA, Macías J, et al. HCV epidemiology in high-risk groups and the risk of reinfection. J Hepatol. 2016;65:S33–45.