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AIDS Rev. 2015;17:231-7

News on HIV-HCV Coinfection: Update From the 2015 GEHEP Conference

Eva Poveda[1], David Wyles[2], Luis Morano[3], Juan Antonio Pineda[4] and Federico García[5] on behalf of GEHEP

[1]Division of Clinical Virology, Instituto de Investigación Biomédica de A Coruña (INIBIC)-Complexo Hospitalario Universitario de A Coruña (CHUAC), Sergas, Universidade da Coruña (UDC), A Coruña, Spain; [2]Infectious Disease Division, University of California, San Diego, USA; [3]Unit of Infectious Diseases, University Hospital Álvaro Cunqueiro, Vigo, Spain; [4]Unit of Infectious Diseases and Microbiology, Hospital Universitario de Valme, Seville, Spain; [5]Department of Microbiology, Instituto de Investigación Biosanitaria (IBIS)-Complejo Hospitalario Universitario de Granada, Granada, Spain

Abstract

New therapeutic options for the treatment of HCV infection are highly effective, possess minimal side effects, and allow for a shortened course of therapy, presenting a favorable scenario to treat and cure all patients chronically infected with HCV. However, there are still many challenges to advancement towards HCV eradication, not only related to the cost and the availability of the drugs, but also pertaining to epidemiologic, diagnostic, and treatment issues that remain to be resolved. Advances in the knowledge of all these topics are essential for the optimization of diagnostic and treatment strategies to fight again HCV infection. The latest data presented at the I Conference of the Group for the Study of Viral Hepatitis (GEHEP) (23-26 September, Spain) highlights relevant progress on many of these fronts for an overview of HCV infection at present. This review summarizes some of the major findings presented and discussed during the conference. **(AIDS Rev. 2015;17:231-7)**

Corresponding author: Eva Poveda, eva.poveda.lopez@sergas.es

Key words

Hepatitis C. HIV. GEHEP.

Introduction

Hepatitis C virus (HCV) remains a global public health problem and is one the leading causes of liver disease worldwide. Chronic HCV infection causes progressive liver damage, which may lead to cirrhosis, hepatocellular carcinoma (HCC), and other HCV-related complications, resulting in the death of more than 350,000 people every year. It is estimated that 130-150 million people worldwide are chronically infected; however, most of them are unaware of their infection[1,2]. Since HCV diagnosis is the first step towards cure, efforts should be made in this regard. Indeed, the recommendation made by the US Centers for Disease Control and Prevention (CDC) for HCV testing has been expanded since 2012 with a birth-cohort-based strategy (persons born during 1945-1965) in addition

Correspondence to:
Eva Poveda
Division of Clinical Virology
Instituto de Investigación Biomédica de A Coruña (INIBIC)
Complexo Hospitalario Universitario de A Coruña (CHUAC)
As Xubias, s/n
15006 A Coruña, España
E-mail: eva.poveda.lopez@sergas.es

GEHEP collaborators:
Karin Neukam, Iria Rodríguez-Osorio, Daniel Navarro, Antonio Aguilera, Natalia Chueca, Nicolás Merchante, Rocío Nuñez-Torres, Miguel García Deltoro, Rafael Granados, Enrique Ortega, Francisco Téllez.

to testing high-risk populations[3]. Of note, the timing and nature of the HCV epidemic is unique across the globe, and thus, each country needs to determine its own HCV seroprevalence by year of birth to identify the optimal target population to implement the appropriate screening programs[4]. Presumably such strategies will identify HCV-infected patients who otherwise would have been missed and that can benefit from current highly effective therapies.

The availability of new drugs globally called direct-acting antiviral (DAA) agents that specifically block various viral proteins including NS3/4A protease, the NS5B polymerase, and the NS5A protein has significantly improved the rates of cure of patients with chronic HCV infection[5,6]. Moreover, these drugs exhibit a good safety profile with minimal adverse events and have shortened the treatment duration to 12 weeks in most cases. Although the overall rates of cure are above 90%, there is still a group of patients who do not achieve sustained virological response (SVR), and these non-response rates may approach 30% in some specific populations (i.e. patients infected by genotype 3 with cirrhosis)[7-9].

There are several factors influencing the clinical response to these therapies. Some can be monitored using molecular biology assays before and/or during treatment such as HCV genotype/subtype, HCV RNA values (IU/ml), or HCV polymorphisms or resistance variants associated with a loss of drug susceptibility[10-12]. When and in whom these parameters must be determined is constantly changing, with updates provided periodically through HCV treatment guidelines incorporating new clinical trial data and drug approvals[13-15]. Another important issue is to establish which are the most accurate assays for the determination of these parameters in clinical practice when using DAA therapies.

There are clinical parameters that may impact the response to different DAA therapies (i.e. fibrosis stage, hepatic function, drug-drug interactions with concomitant medications) that need to be taken into consideration[16]. Moreover, recently, the identification of single nucleotide polymorphisms (SNP) associated with treatment response, as well as liver disease progression (i.e. IL-28, ITPA, PNPLA3)[16-18] may have clinical relevance. Lastly, it is critical to produce data on safety and efficacy from the use of DAAs in real-life.

New data regarding these topics, including HCV epidemiology, clinical trials, and real-life experience evaluating DAA-based therapies, along with developments in diagnostic tools to monitor the clinical response, were presented at the I Conference of GEHEP held in Vigo, Galicia, Spain on September 23-26, 2015[19]. This review summarizes the main issues discussed at this event.

HCV epidemiology

In the DAA era, HCV genotype and subtype (1a and 1b) must be assessed prior to treatment initiation as these results are one of the main factors driving the choice of therapy[13-15,20]. In Spain, but also more broadly in Europe, updated information regarding HCV epidemiology, especially on HCV genotype/subtype prevalence and distribution in specific populations[21-23], is lacking. Two relevant studies on these topics were presented at the conference.

Navarro, et al.[24] reported data on the distribution of HCV genotypes in Spain during the period 2011-2015. This was a retrospective study recruiting 15,140 patients from 24 hospitals from nine different geographic regions in Spain. The annual distribution of HCV genotypes and subtypes as well as gender, age, transmission route, HIV and/or HBV coinfection, and treatment were recorded. The most prevalent genotype was G1 (68.8%), 27% G1a and 35.9% G1b, followed by G3 (16.5%) and G4 (11.9%). The less-represented genotypes were G2 (2.7%) and G5 and 6 (0.1%) (Fig. 1). HCV G1a, 3 and 4 were closely associated with male gender, parenteral route of transmission, and coinfection with HIV and/or HBV. Conversely, G1b was associated with female gender, non-parenteral route of transmission, and monoinfection. Different genotype distribution was observed based on age and geographic region in Spain (center vs. north/south). Of note, a significantly higher prevalence of G1b was observed in individuals older than 70 years compared with those under 50 years (83.6 vs. 21.8%). Moreover, a significantly higher prevalence of G1a, 3, and 4 was observed in subjects under 50 years (32.3, 19.8, and 16.0%, respectively). Regarding the geographic distribution, a higher prevalence of G1b was observed in central Spain (43.6%) compared with the north (29.9%), while G3 is less represented (11.7%) centrally. Finally, the primary method employed for HCV genotyping was the line probe assay (LiPA 2.0 Siemens) (42.9%) followed by the real time PCR commercial assays of Roche (20.1%) and Abbott (18.2%).

The other major study was presented by García, et al.[25] and reported the distribution of HCV genotypes in several European regions. This was also a retrospective study recording epidemiological information and HCV genotype data from HCV-infected patients who underwent HCV genotyping between 2011-2015 in

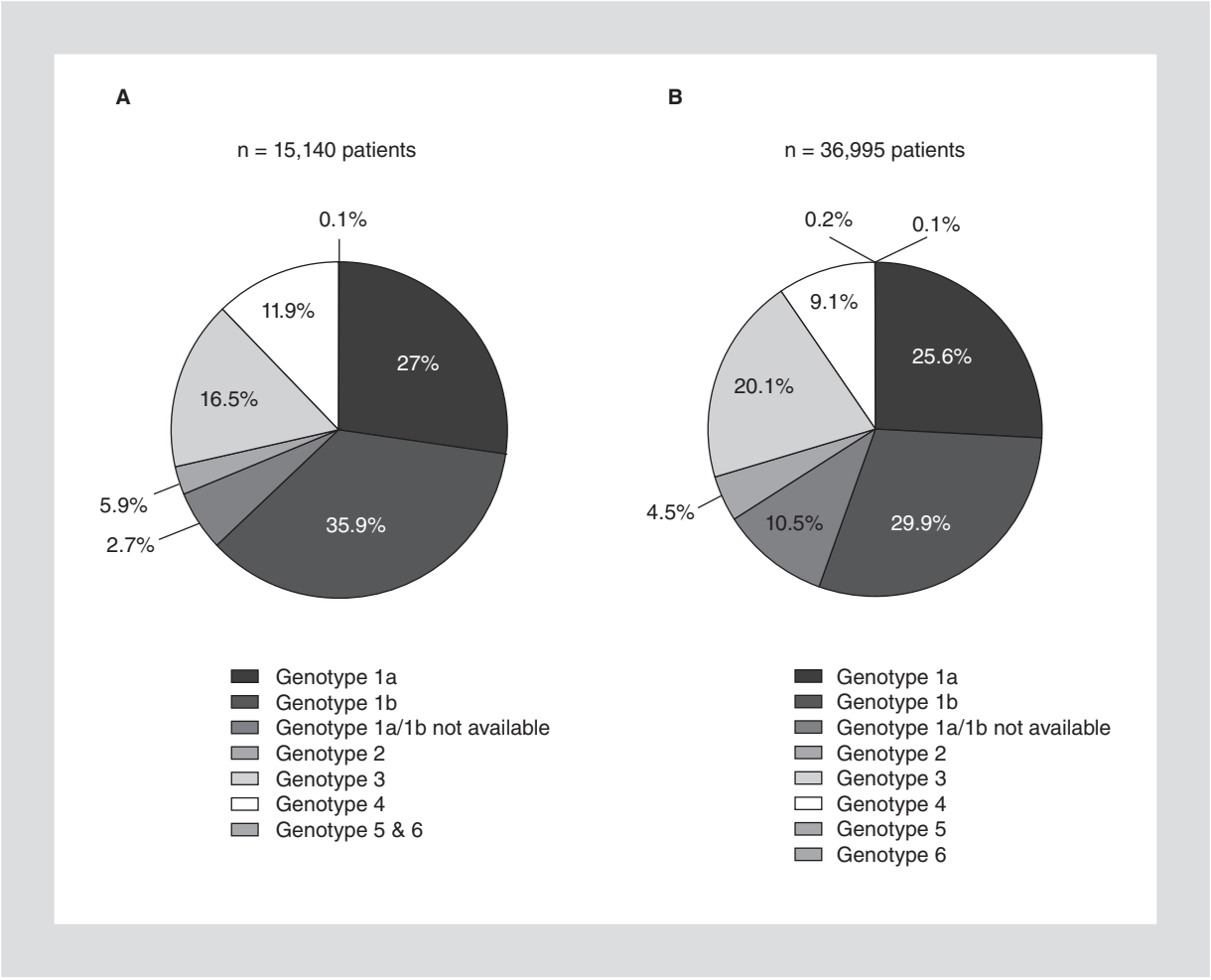

Figure 1. *Distribution of HCV genotypes in Spain* ***(A)*** *and Europe* ***(B)*** *during the period 2011-2015.*

53 European centers. A total of 36,995 patients were included in the study. The most prevalent genotype was G1 (66.1%; 41.6% G1a and 55% G1b) followed by G3 (20.1%) and G4 (9.1%). The less-represented genotypes were G2 (4.5%), G5 (0.2%)%, and G6 (0.1%) (Fig. 1). Although the genotype distribution was quite similar in all participating countries, some variations were observed: (i) Russia with a lower proportion of G1 (50.8%) and higher G2 (11.2%) and G3 (37.9%); (ii) Italy, with higher proportion of G2 (Catanzaro 23.9%, Rome 13.6%); and (iii) Spain, with a higher prevalence of G4 (11.9%). In older patients (≥ 65 years old) a significantly larger proportion of G1b was observed, while in younger patients, mostly infected via drug abuse and/or tattooing, G1a was most prevalent (33.5%) followed by G3 (30%). In the context of presumed sexual transmission, a higher proportion of G4 was recognized, being the most prevalent among men who have sex with men (MSM, 28.9%). HIV coinfection was significantly associated with higher proportions of G1a and G4.

Acute HCV infection is another topic worth mentioning, and is largely due to the epidemics of acute HCV infection described in different countries worldwide among HIV-infected MSM. At the conference, Quintana, et al.[26] retrospectively evaluated episodes of acute HCV infection at eight hospitals in southern Spain. A total of 23 cases of acute HCV infection were detected between 2004-2014. These figures show a low number of HCV acute infections without evidence of an increase over time. These data contrast with those from other European cities (e.g. London, Amsterdam) in which outbreaks of acute HCV infection have been reported[27,28]. The reasons for the lack of an epidemic outbreak in the south of Spain compared with other European regions are unknown. Further studies are needed to clarify these different epidemiologic patterns.

HCV therapy

HCV clinical trials

New data related to the safety and efficacy of the combination ledipasvir/sofosbuvir (LDV/SOF) in different HCV populations was presented. First, Morano, et al.[29] presented the results of the ION-4 study which evaluated the safety and efficacy of a single tablet regimen of LDV/SOF in HCV genotype 1 or 4 patients coinfected with HIV-1. A total of 335 patients were enrolled in the study, with the following HCV genotype distribution: 75% G1a, 23% G1b, and 2% G4. The overall SVR at 12 weeks was 96.6% among non-cirrhotic patients and 94% among cirrhotic patients. There were no discontinuations due to adverse events and the combination was generally well tolerated.

A shortened duration of LDV/SOF for eight weeks ± ribavirin was compared to 12 weeks of LDV/SOF in non-cirrhotic G1 treatment-naive patients (ION-3, n = 647). The overall SVR rates were non-inferior between the eight and 12 week LDV/SOF arms; however, relapse was numerically higher in those treated for eight weeks compared to 12 weeks (5.1 vs. 1.4%, respectively). A *post hoc* analysis of this study evaluating the baseline factors that might be responsible for the differential relapse rates between the two non-ribavirin containing arms was presented by Wyles, et al.[30] at the conference.

For this purpose, historical negative predictors of treatment response were evaluated in the study population at baseline in patients who relapse, including: age, gender, race, G1, METAVIR fibrosis stage, body mass index, interleukin (IL)-28 status, and baseline HCV RNA. Interestingly, the majority of failures in ION-3 who were treated for eight weeks had a baseline HCV RNA greater than 10 million IU/ml. Although higher overall rates of relapse were observed for males and subjects who were IL-28 non-CC genotype, these parameters had no effect on outcomes among those patients with a pre-treatment HCV RNA < 6 million IU/ml. Therefore, a baseline HCV RNA < 6 million IU/ml in treatment-naive, non-cirrhotic G1 patients correlated with similar SVR and relapse rates with eight or 12 weeks of LDV/SOF. This shortened-duration treatment strategy might improve adherence and affordability of HCV treatment.

Real-life experience with direct-acting antivirals

Several studies evaluating the safety and efficacy of DAA-based therapies in clinical practice in specific patient populations (i.e. HIV coinfected, elderly) attending Infectious Diseases Units in Spain were presented at the conference.

Neukam, et al.[31] evaluated the impact of HIV coinfection on the safety and efficacy of DAA-based therapies in a prospective multi-cohort study of HIV/HCV-coinfected patients (HEPAVIR-DAA cohort) and HCV-monoinfected individuals (GEHEP-MONO cohort) who initiated any DAA-containing therapy at the infectious diseases units of 22 hospitals throughout Spain. The majority of the 683 patients included in the study initiated an interferon-based therapy, mainly based on telaprevir (72.9%). Overall rates of SVR at week 12 in subjects with and without HIV coinfection were 54.2 vs. 76.7% in an on-treatment approach. Overall, 10.7% of patients discontinued therapy without differences between HIV/HCV-coinfected and HCV-monoinfected subjects. The multivariate analysis identified HIV infection as an independent, negative predictor of SVR at week 12. The negative impact of HIV infection in the response to DAA-containing therapy observed in this study population might be driven by a more advanced degree of liver damage in the group of HIV/HCV coinfected.

New DAAs are highly safe and well tolerated as part of interferon (IFN)-free regimens against HCV infection. Therefore, elderly patients, defined as over 65 years old, in whom comorbidities and concomitant chronic medications are frequent, might benefit from these therapies. However, there is scarce data regarding the effectiveness and safety of these new drugs among elderly patients as this population is underrepresented in clinical trials. Rodríguez-Osorio, et al.[32] evaluated the safety of DAA IFN-free therapies in 32 HCV-monoinfected patients over 65 years of age in clinical follow-up in a hospital in the northwest of Spain. Most were female (67%) with a mean age of 70 years, infected with G1b (79%), and 70% had cirrhosis. The majority of the regimens included ribavirin (RBV, 61%; dose based on body weight) with LDV/SOF, SOF/simeprevir, and paritaprevir/ombitasvir/dasabuvir being the most commonly used combinations. Adverse events were frequent (55%) and the majority (82%) had concomitant medication with 27% requiring adjustment. Moreover, in one-third of patients receiving RBV a dose reduction was required. These findings highlight that elderly patients (> 65 years) who initiate a DAA-based therapy require special consideration, in particular with regards to RBV-dose adjustment and the management of drug-drug interactions.

The experience with the use of sorafenib in a cohort of HIV-infected patients for the treatment of HCC was

reported by Merchante, et al.[33] in a multicenter study (32 centers) within the HCC-GEHEP cohort. The study was performed in 35 HIV-infected patients. Median duration of sorafenib treatment was 60 days, and 83% of patients had died by the end of the study. Adverse events of any grade were recognized in 57% of patients. Overall, the efficacy and tolerability of sorafenib in HIV-infected patients in real-life conditions appears significantly lower than what has been reported in registration clinical trials.

HCV diagnostic tools and prognosis factors

The advent of DAAs has identified new factors influencing clinical response. HCV genotype 1 subtype (1a vs. 1b) is a prime example. Combined data from clinical trials demonstrate a lower response for the majority of DAAs (including NS3/4A, NS5B non-nucleoside and NS5A inhibitors) among HCV G1a compared to G1b patients[34-36]. These data have made accurate subtype determination critical for all clinicians and the diagnostic laboratories serving them prior to treating HCV-infected patients.

There are several different commercial assays available for HCV genotyping. The accuracy of these assays was evaluated by the GEHEP group (Chueca, et al.) in 308 clinical samples[37]. TRUGENE-HCV genotyping kit (Siemens), VERSANT HCV Genotype 2.0 assay (LIPA-Siemens), and RealTime HCV Genotype II (Abbott) were evaluated with comparison to NS5B sequencing as the reference standard[38-40]. TRUGENE failed to correctly assign HCV genotype in up to a third of cases with more than 15% of the errors being the attributable to 1a/1b-related misclassifications. VERSANT HCV genotype 2.0 assay misclassified HCV subtype in 10% of cases, while Abbott RealTime HCV Genotype II assay properly assigned all genotype 1 subtypes, although it was not able to reliably discriminate between subtypes for genotypes 2, 3, 4, and 5. Since the VERSANT HCV assay is one of the more frequently used in Spain, these results raise some concerns regarding the methodology currently in use for HCV genotyping.

Recent discoveries have highlighted the influence of host genomics on HCV outcomes and progression of liver disease. This is the case with the recognition of the impact of SNPs within the IL-28B gene that are strongly associated with both natural clearance and treatment responses of HCV to pegylated-IFNα-RBV[16]. There are other SNPs under evaluation and some of them have been associated with liver disease progression, steatosis, hematological side effects, and metabolic disorders (i.e. PNPLA3, ITPA)[16,18]. Some studies of host genetic factors were presented at the conference pertaining to the impact of specific polymorphisms on fatty liver disease in HIV-infected patients. Nuñez-Torres, et al.[41] evaluated the impact of 19 SNPs associated with non-alcoholic fatty liver disease in HIV-infected individuals. A total of 431 HIV-infected patients were included in this study and 41.5% had evidence of fatty liver disease. Two SNPs, LPPR4 and SAMM50, were independent risk factors for fatty liver disease and steatohepatitis development, respectively, among HIV-infected individuals. Moreover, variation within the Fatmass and obesity associated (FTO) gene has been identified as a predictor of fatty liver disease in HIV-infected patients independent of metabolic factors.

Merchante, et al.[42] identified liver stiffness as a predictive factor of variceal bleeding in HIV/HCV-coinfected patients with compensated cirrhosis. The study was performed in a prospective cohort of 446 HIV/HCV-coinfected patients with a new diagnosis of cirrhosis, based on the presence of liver stiffness > 14 kPa and no previous decompensation of liver disease. All patients underwent an upper gastrointestinal endoscopy (UGE) for the screening of esophageal varices at entry in the cohort before November 2009. From this date, UGE was not recommended by the cohort protocol in patients with liver stiffness < 21 kPa. The authors concluded that no individual with baseline liver stiffness < 21 kPa presented a variceal bleeding episode, and therefore UGE can be safely avoided in these patients.

Merchante, et al.[43] also evaluated prognostic factors for the development of HCC in HIV-infected patients within the HCC-GEHEP cohort. Since 1996, 281 HCC cases have been diagnosed in HIV-infected patients in the 32 centers. The HCC was related with HCV-infection in 63% of patients. From these, 62% received therapy against HCC and 72% died, with a median survival time after diagnosis of five months. Detectable HIV viral load together with liver-related factors, such as baseline alpha-fetoprotein level > 200 ng/dl and a higher Barcelona clinic liver cancer (BCLC) stage were predictors of worse outcomes.

Conclusions

The new era in the treatment of HCV infection with highly active IFN-free combinations possessing minimal side effects and shortened treatment durations (12 weeks in most cases) bring new epidemiologic, diagnostic, and

treatment challenges to bear on the goal of achieving HCV eradication. The epidemiologic data presented in this conference highlights key differences in the distribution of HCV genotypes in Europe by both geographic and demographic variables such as region and patient age, gender, and/or route of transmission. Of note, genotype 3 was recognized as the second most prevalent HCV genotype, accounting for more than 20% of HCV infections and reaching 30% in elderly patients. Since genotype 3 is currently the hardest to treat, and also possess a more aggressive clinical course, its management will require a special effort. A shortened duration of treatment to eight weeks might be possible for HCV genotype 1, treatment-naïve, non-cirrhotic patients with baseline HCV RNA below 6 million IU/ml.

HIV/HCV-coinfected patients might benefit from IFN and RBV-free highly effective and well-tolerated therapies, administered once daily for 12 weeks, even in the setting of cirrhosis (though in general, established treatment guidelines should be followed). More data from real-life experiences with IFN-free combinations are needed. Data presented in elderly patients (> 65 years) provided a cautionary tale on an enhanced need for RBV dose reductions and drug-drug interaction monitoring in this population. Misclassification of HCV genotype, and particularly subtype, using commercial assays (15%) opens a debate about the methodology that should currently be used for HCV genotyping in Spain and beyond. The identification of SNPs as biological markers for liver disease including fibrosis progression or even regression in HCV-infected patients is a line of research that is gaining more interest. Additional data in large cohorts will be required to obtain conclusive results with the potential for implementation in clinical practice. Altogether, these data provide relevant information to advance the fight against HCV infection.

Declaration of interest

All authors declare no conflicts of interest.

This work was supported in part by grants from Fondo de Investigación Sanitaria (CPII14/00014, PI10/02166, PI13/02266, CM13/00328), and Fundación Profesor Novoa Santos, A Coruña, and RD12/0017/006 (Plan Nacional de I+D+I and Fondo Europeo de Desarrollo Regional-FEDER). Federico García has received a research extension grant from the Programa de Intensificación de la Actividad de Investigación del Servicio Andaluz de Salud. Juan Antonio Pineda is the recipient of an intensification grant from the Instituto de Salud Carlos III (Programa-I3SNS).

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