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Characterization of chronic HCV infection in Northwest Spain: Impact of the treatment strategic plan of the Spanish National Health Service on HCV cure

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Abstract
The aim of the study was to characterize HCV infection in Northwest Spain and assess the impact of the Spanish Strategic Plan to cure HCV infection. Overall, 387 patients were included (60.9% HIV/HCV coinfected and 28.2% cirrhotic). Of these, 72.9% of patients that were recognized as priority for HCV treatment according to the Spanish Strategic Plan (≥F2, transplant or extrahepatic manifestations), initiated treatment during 2015. Globally, SVR12 was achieved in 96.5% of patients. The implementation of the Spanish Strategic Plan has been critical to advance in HCV cure, but 27.1% of priority patients still remain awaiting HCV treatment initiation.

Keywords
HCV infection, HCV treatment, HIV/HCV coinfection

1. BACKGROUND

HCV infection is an important health problem affecting more than 150 million people worldwide and about 475 000 people in Spain,[1][2] and can lead to significant morbidity and mortality.[3] The introduction of high-effective and well tolerated direct-acting antivirals (DAA) has allowed for shorter treatment regimens and offered new opportunities for previously excluded groups. Additionally, these newer regimens have shown to be cost-effective across all fibrosis stages.[4, 5] However, their current high cost only allows a restricted number of patients to access treatment. In May 2015, the Spanish National Health Service published a Strategic Plan to face HCV infection. The objective of this Plan was to effectively address the prevention, diagnosis, treatment, and monitoring of HCV-infected patients.[2]

The aim of the study was to characterize HCV infection in Northwest Spain and evaluate the impact of the Spanish Strategic Plan in this population.

2. MATERIALS AND METHODS

This is a transversal observational study. Patients with chronic HCV infection in two hospitals of Northwest Spain were included in the period June 2014 to December 2015 ($n = 387$). This sample size allows to estimate parameters of interest with a confidence interval of 95% ($\alpha = 0.05$) and a precision ±5%.

The research protocol was approved by the regional ethics committee ("Comité Ético de Investigación Clínica de Galicia," register code 2013/249). All patients participating in the study signed the informed consent.

Epidemiological, clinical, and virological characteristics were recorded. Liver fibrosis was measured by transient elastography. Regimen and duration of treatment were recorded in those patients who initiated HCV treatment during 2015. Treatment efficacy was measured as sustained virological response (SVR12) defined as HCV-RNA below the level of detection recorded 12 weeks after treatment discontinuation.

The statistical analysis was performed using the Statistical Package for the Social Sciences software (SPSS 19.0, Chicago, IL). Categorical variables were presented as number of cases or percentage and compared by X^2 test or Fisher's exact test, when appropriate. Continuous variables were expressed as median (interquartile range) and compared by non-parametric Mann-Whitney and Kruskal-Wallis test, when appropriate. A P-value <0.05 was considered statistically significant.

3. RESULTS

A total of 387 patients were included. Of these, 72.6% were men; 60.9% ($n = 223$) HIV/HCV coinfected patients and 28.2% ($n = 100$) cirrhotic. Epidemiological, clinical, laboratory parameters, and virological characteristics previous to HCV-treatment initiation are shown in Table 1. Genotype 1 was the most common one (66.2%) followed by genotype 3 (16.8%). Overall, 4.4% of patients had previous hepatic decompensation: hydropic decompensation (3.9%), encephalopathy (1.3%), and/or gastrointestinal bleeding (0.8%). In addition, 1% of patients had hepatocellular carcinoma and 3.9% extrahepatic manifestations of HCV infection. Among treatment-experienced (34.4%) patients, 81.8% had received pegylated-interferon (Peg-IFN) and ribavirin (RBV) regimen, and 15.2% Peg-IFN + RBV + boceprevir/telaprevir. Response to previous HCV treatment was: 31.8% null response, 25.8% relapse, 21.2% intolerance to Peg-IFN + RBV, 10.6% partial response, and 10.6% unknown response.

Table 1. Epidemiological, clinical, and virological characteristics of HCV infection and DAA-regimens used to treat HCV infection during 2015

Characteristics	HCVmono ($n = 143$)	HIV/HCV ($n = 223$)	*P*	Total ($n = 387$)
Median time with HCV infection (IQR), years	15 (8-19)	18 (13-23)	< 0.001	17 (11-21)
Median age (IQR), years	50 (43-55)	49 (44-53)	0.163	49 (45-54)
Male sex (%)	75.5	74	0.742	72.6
Route of transmission (%)			< 0.001	
IDU	44.8	85.7		69.7
Not known	47.6	7.6		23.2
Other	7.7	6.7		7.1
Median AST (IQR), mg/dL	37 (26-59)	42 (30-65)	0.051	39 (28-61)
Median ALT (IQR), mg/dL	47 (25-88)	46 (32-78)	0.595	45 (29-78)
HBsAg (%)	0	0.5	0.999	0.3
Prior HCV treatment (%)			0.901	
Naive	65.7	66.4		65.6
Treatment-experienced	34.3	33.6		34.4
Median HCV-RNA (IQR), log10 UI/mL	6.01 (5.03-6.48)	6.21 (5.59-6.65)	0.007	6.13 (5.24-6.58)
IL-28B polymorphism (%)			0.019	
CC	24.3	41.5		36.3
CT	61.4	42.1		47.9
TT	14.3	16.5		15.8
HCV genotype (%)			0.001*	
1a	43	41.7		41.5
1b	30.3	16.1		23.1
1 no subtype	0.7	1.3		1.6
2	3.5	0.4		1.8
3	13.4	20.6		16.8
4	9.2	19.7		15.3
Liver fibrosis (%)			0.364	
F0-F1	29.2	38.5		34.4
F2	24.6	20		22
F3	16.9	14.6		15.5
F4	29.2	26.8		28.2
Median liver fibrosis (IQR), KPa	8.8 (6.9-14.5)	8.5 (6.1-13.4)	0.299	8.7 (6.3-14.3)
HCV treatment during 2015 (%)	64.3	42.4	< 0.001	52.7
Regimen of treatment (%)				
DAA (SOF or SMV) + Peg-IFN + RBV	6.5	0		2.9
SOF + DAC ± RBV	14.1	25.5		18.6
SOF + LDV ± RBV	43.5	59.6		51
SOF + SMV ± RBV	9.8	8.5		10.3
SOF + RBV	6.5	0		3.4
3D	15.2	2.1		10.3
2D	4.3	1.1		3.4
Duration of treatment (%)			0.103**	
8 weeks	1.1	0		0.5
12 weeks	74.4	64.5		70.6
24 weeks	24.4	35.5		28.9

HCVmono, hepatitis C monoinfection; IQR, interquartile range; IDU, intravenous drug users; AST, aspartate aminotransferase; mg, miligrams; dL, decilitre; ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen; HCV-RNA, plasmatic viremia of HCV; F0-F4, grade of liver fibrosis measured by transient elastography; KPa, kilopascals; DAA, direct-acting antivirals; SOF, sofosbuvir; SMV, simeprevir; Peg-IFN, pegylated interferon; RBV, ribavirin; DAC, daclatasvir; LDV, ledipasvir; 3D, ombitasvir + paritaprevir/ritonavir + dasabuvir; 2D, ombitasvir + paritaprevir/ritonavir.
*Comparing genotypes 1a, 1b, 3, and 4.
**Comparing 8-12 versus 24 weeks.

Regarding HIV/HCV patients, 95.9% received antiretroviral treatment (ART) with a combination of two nucleoside reverse transcriptase inhibitors and a protease inhibitor (43.8%), a non-nucleoside reverse transcriptase inhibitor (28.8%) or an integrase inhibitor (13.5%) while 13.5% received other regimens. Median CD4 count at the moment of the study was 566 (312-750) cells/mm^3 and 86.7% of patients under ART had suppressed viremia.

During 2015, 52.7% of HCV-infected patients initiated treatment. According to the Spanish Strategic Plan for HCV infection, 66.5% of all patients should be prioritized for HCV treatment (liver fibrosis ≥F2, transplant or extrahepatic manifestations). Of these, 72.9% initiated HCV treatment during 2015. Combinations of DAA and duration of HCV treatment are shown in Table 1.

Overall, 96.5% of HCV patients achieved SVR12. SVR12 rates in different subgroups are shown in Figure 1. No differences were observed according to previous HCV treatment ($P = 0.086$), HIV/HCV coinfection ($P = 0.395$), HCV genotype (1 vs. non-1 genotype, $P = 0.999$; and 3 vs. non-3, $P = 0.181$) or liver fibrosis (F2-F3 vs. F4, $P = 0.408$).

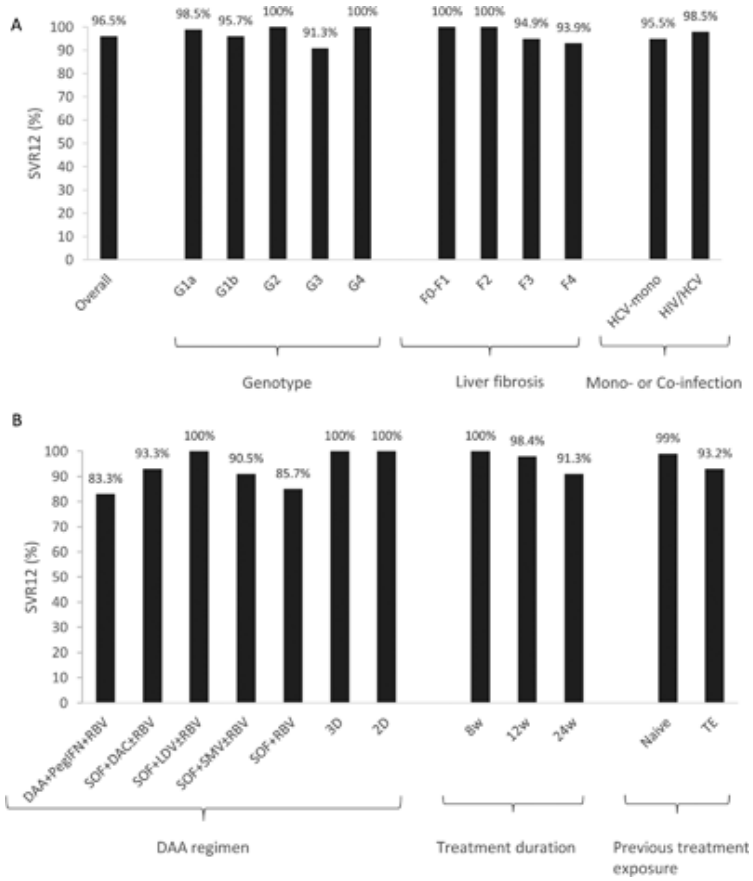

Figure 1. Sustained virological response at 12 weeks (SVR12) after finishing HCV treatment. A: Global SVR12 and SVR12 according to genotype, liver fibrosis and HIV/HCV coinfection. B: SVR12 according to DAA-based regimen, duration of HCV treatment and previous exposure to HCV treatment. G1a, genotype 1a; G1b, genotype 1b; G2, genotype 2; G3, genotype 3; G4, genotype 4; F0-F1, liver fibrosis measured by transient elastography <7.5 KPa; F2, liver fibrosis measured by transient elastography 7.5-9.4 KPa; F3, liver fibrosis measured by transient elastography 9.5-12.5 KPa; F4, liver fibrosis measured by transient elastography >12.5 KPa; HCV-mono, HCV mono-infected patients; HIV/HCV, HIV and HCV coinfected patients; DAA, direct-acting antivirals (includes SOF or SMV); PegIFN, pegylated interferon; RBV, ribavirin; SOF, sofosbuvir; DAC, daclatasvir; LDV, ledipasvir; SMV, simeprevir; 3D, ombitasvir + paritapevir/ritonavir + dasabuvir; 2D, ombistasvir + paritaprevir/ritonavir; 8 w, 8 weeks of HCV treatment; 12 w, 12 weeks of HCV treatment; 24 w, 24 weeks of HCV treatment; TE, previous treatment-experienced HCV patients

Among failures ($n = 6$), five were treatment-experienced (Peg-IFN-based regimens), four cirrhotic, and one was HIV/HCV coinfected. Regarding HCV genotypes, there were four patients with genotype 1 (only one with genotype 1a although subtype was not determined in one patient) and two with genotype 3. All failures but two (intolerance to Peg-IFN-based regimen and hepatic decompensation with death) were relapses. Of these, three patients were re-treated (Peg-IFN + RBV + sofosbuvir (SOF) and SOF + ledipasvir + RBV, and both achieved SVR12 while another is on-treatment with SOF + daclatasvir + RBV) and one patient died before re-treatment due to hepatocellular cancer. Resistance test was performed in only one patient and no resistance mutations were found.

4. DISCUSSION

This study characterizes chronic HCV infection in 387 patients in Northwest Spain and the impact of the Spanish Strategic Plan on HCV cure last year. This cohort had 28.2% of patients with cirrhosis and a high prevalence of HIV/HCV patients (60.9%). The introduction of the Spanish Strategic Plan in 2015 has allowed to treat half (52.7%) of all HCV patients with different DAA-combinations and SVR12 rates over 96%.

The distribution of HCV genotypes is similar throughout Western Europe with some local differences.[1, 6-8] The prevalence of HCV infection in Spain is among the highest in Europe and several studies reported genotype 1 as the most common one, similarly to our cohort (66.2%).[9-11] In addition, HCV genotypes are usually associated to different routes of transmission. In fact, genotypes 1a, 3, and 4 are more common among intravenous drug users[1, 6-8, 10, 12] and represent 82% of HIV/HCV patients in our cohort.

Cirrhosis had similar prevalence in both HCV-monoinfected and HIV/HCV patients (29.2% vs. 26.8%, respectively). Since the widespread introduction of ART regimens, data on the effect of HIV coinfection on liver fibrosis progression and its complications have been controversial.[13-16] An improved control of HIV infection with earlier initiation of a less hepatotoxic ART and higher CD4 counts could explain similar rates of cirrhosis in both HCV-monoinfected and HIV/HCV patients observed in our cohort.

The development of DAA has allowed a significant improvement in rates of SVR12. However, those patients involved in clinical trials tend to have more favorable outcomes than patients in the real-world mainly due to strict patient selection. In our cohort, rates of SVR12 were consistently high across all subgroups evaluated, ranging from 83.3% to 100%. Cirrhosis and HIV/HCV coinfection had been previously identified as independent predictors of virological failure.[17] However, we found no significant differences in SVR12 based on HIV/HCV coinfection or liver fibrosis. Despite the high rate (98.5%) of SVR12 observed in our cohort of HIV/HCV patients, it is noteworthy that less patients have initiated treatment compared with HCV-monoinfected (42.4% and 64.3%, respectively). Effectiveness in HIV/HCV patients was similar to HCV-monoinfected and concordant with clinical trials and real-world published data.[5, 18] Therefore, HIV/HCV population appear to be no longer a hard-to-treat population and should be treated as HCV-monoinfected patients.[19]

In this scenario, the eradication of HCV infection is a desirable and achievable goal for the next years. A successful treatment results in curing HCV infection and decreasing the risk of HCV-related complications.[20] However, enthusiasm for efficacy and safety of DAA has been dampened by their high price and some countries have restricted these therapies to advanced-stage patients. This is the case of Spain, where the implementation of the Strategic Plan to face HCV infection recommends the priority of HCV treatment for those patients with liver fibrosis ≥F2, transplant or extrahepatic manifestations. According to this, 66.5% of our cohort should be prioritized and 72.9% of these patients initiated HCV treatment during 2015.

This study has some limitations. The high prevalence of HIV/HCV coinfected patients could represent a selection bias and safety of HCV treatment was not evaluated.

In summary, the Spanish Strategic Plan has had a great impact on our medical area because it has allowed to treat half of all HCV-infected patients and almost 75% of patients who were candidates to prioritize HCV treatment. Effectiveness was very high and similar to that observed in the context of clinical trials, including cirrhotic and HIV/HCV coinfected patients. Therefore, access to DAA will probably allow to avoid HCV-related morbidity and costs of HCV complications.

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CONFLICTS OF INTEREST

All authors declare no conflicts of interest.

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