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Profiles and clinical management of hepatitis C patients in Spain: disHCovery study

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ABSTRACT

Introduction. To assess the clinical profile and management of patients with hepatitis C (HCV) infection in an observational study in Spanish hospitals.

Methods. The study included an initial cross-sectional phase (study phase I), in which investigators at 48 hospitals from 14 Spanish regions collected data from approximately 20 consecutive patients each (a total of 1,000 patients) to assess the general features of HCV-infected patients of any genotype. During the second phase (study phase II), data from 878 patients that were infected exclusively with genotype 1 HCV were assessed retrospectively. Eight pre-defined clinical profiles were established, in order to assess clinical and previous treatments characteristics.

Results. Among the HCV-infected individuals that were analysed during the first part, HCV genotype 1 was found to be predominant (with a prevalence of 76.6%), prevailing the subtype 1b (69.8%), with other significant groups infected by genotype 3 (12.3%) and 4 (7.4%). In the second part of the study, 44% of the HCV genotype 1-infected patients were at a F3/F4 fibrosis stage. 15.9% had never been treated, and previously unsuccessfully treated patients that were no longer receiving anti-HCV treatment accounted for 50.8% of cases. Individuals with a sustained virologic response (SVR) to previous dual therapies (based on Interferon and Ribavirin) were only 14.5% and patients under treatment during the study accounted for the remaining 18.8%. A total of 713 patients (81.2%) in the second phase were not receiving any type of therapy over the period analysed, mainly due to the anticipation of new anti-HCV drugs (41.8%), SVR achievement (17.8%) and unresponsiveness to therapies available at the time of the study (9.5%).

Conclusions. HCV genotype 1, predominately 1b, is the most prevalent type in Spain. Advanced fibrosis or cirrhosis is frequent in this group, mainly patients not yet cured.

Key words: Chronic hepatitis C, genotype 1, risk factors, epidemiological study, clinical profiles, interferon, ribavirin.

Perfil clínico y seguimiento de los pacientes con hepatitis C crónica en hospitales españoles: Estudio disHCovery

RESUMEN

Introducción. Evaluar el perfil clínico y el manejo de los pacientes con infección por hepatitis C crónica (VHC) en un estudio observacional en hospitales españoles.

Métodos. El estudio incluye una fase inicial de registro transversal de datos agregados (primera fase del estudio) en la cual investigadores de 48 hospitales en 14 regiones diferentes de España recopilaron datos de aproximadamente 20 pacientes atendidos consecutivamente en consulta (un total de 1.000 pacientes) en los que se analizó, en cada uno de ellos, las características generales de la infección por VHC de cualquier genotipo. Durante la segunda fase del estudio se realizó una evaluación retrospectiva de datos procedentes de 878 pacientes exclusivamente portadores del genotipo 1 del VHC. Se establecieron ocho perfiles clínicos predefinidos con el objetivo de evaluar las características tanto clínicas como de los tratamientos previos.

Resultados. Entre los pacientes con infección por VHC que fueron analizados durante la primera parte del estudio, se observó que el genotipo 1 del VHC era el más frecuente (con una prevalencia del 76,6%), predominando el subtipo 1b (69,8%) seguido de los genotipo 3 (12,3%) y genotipo 4 (7,4%). En la segunda parte del estudio se observó que el 44% de los pacientes infectados por genotipo 1 del VHC presentaban un grado de fibrosis F3/F4. Un 15,9 % de los pacientes no habían sido previamente tratados y un 50,8% habían fracasado a un tratamiento previo y en ese momento no recibían ningún tra-

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tamiento. Un 14,5% de los pacientes habían presentado previamente respuesta viral sostenida (RVS) tras terapia con interferón y ribavirina y durante el punto de corte de estudio se encontraban bajo tratamiento el 18,8% de los pacientes en seguimiento. En la segunda fase, un total de 713 pacientes (81,2% de la población evaluada) no estaba recibiendo tratamiento, debido fundamentalmente a la previsión de llegada de nuevos fármacos (41,8%), a que ya estaban en RVS (17,8%) o a la ausencia de respuesta a las terapias disponibles en el momento del estudio (9,5%).

Conclusiones. El genotipo más prevalente del VHC en España es el genotipo 1, predominantemente 1b. El perfil de paciente más frecuente fue el que presentaba fibrosis avanzadas o cirrosis, principalmente en pacientes aún no curados.

INTRODUCTION

Hepatitis C virus (HCV) infection is a leading cause of chronic liver disease, end-stage liver disease, and liver transplantation¹. Subjects recently infected with hepatitis C virus (HCV) are usually asymptomatic, but early detection of HCV infection is crucial to prevent liver fibrosis, cirrhosis and hepatocellular carcinoma (HCC).

The infection is often detected incidentally during blood donation or other routine medical examinations. A recent epidemiological study reported that from 1990 to 2005 the number of individuals with HCV-specific antibodies has increased from over 122 million to over 185 million people, representing an increase in prevalence from 2.3% to 2.8%². In Spain, chronic infection with HCV is not only an important cause of morbidity and mortality, but it is also the primary cause of liver cirrhosis, far surpassing alcohol-related liver disease³. A study examining causes of death in 2000 obtained from the National Statistics Institute revealed that in Spain hepatitis C was the cause of 4,342 deaths, with 70% of all deaths due to HCC, and 50% of liver cirrhosis-related deaths⁴. Importantly, accurate diagnosis of HCV infection and early administration of antiviral therapy would substantially reduce HCV-associated mortality⁵. Recently, Aleman et al⁶ demonstrated that the incidences of HCC, any liver complication, liver-related deaths, and overall death were significantly lower in patients who achieve a sustained virologic response (SVR) compared to non-SVR and untreated patients. Also, chronic HCV infection has a relevant impact on the patient's quality of life⁷.

The seroprevalence of HCV infection in Spain varies between 1% and 2.6%, based on data obtained from various survey studies conducted in the 1990s. Given the high chronicity rate of HCV in the general population and among high-risk groups (75%), it has been estimated that the number of people infected with HCV nationwide might vary between 480,000 and 760,000³. The full magnitude of the problem posed by chronic HCV infection is difficult to ascertain, although data from the National Epidemiological Surveillance Network (which probably underreports the prevalence) estimate that there are approximately 4,600 cases of acute hepatitis C with

clinical expression annually in Spain. A progressive decrease in the incidence of HCV infection has been observed in recent years, associated with preventive measures and recommendations to minimize transmission through parenteral and potential non-parenteral routes⁸.

On the other hand, there is a lack of data on the current status of patients already diagnosed with chronic hepatitis C in Spain. Some patients have been already treated, both successfully and unsuccessfully; many show a progressive, more advanced disease and additionally, immigration flows have changed the epidemiological characteristics of the disease.

Moreover, in the past years, while promising data regarding novel treatment options for hepatitis C started to reach the stage and new treatments with direct acting antivirals (DAA) were introduced, treatment strategies have changed. In some situations, an option might have been to delay current available treatments waiting for future promising more effective and better tolerated, but uncertainly available, options ("warehousing"). In other scenarios, a decision to prioritize treatments to more advanced liver disease stages, particularly F3 and F4 patients, especially in an economic recession setting, difficults a broad access to drugs in a mainly government-financed healthcare system, limiting the access to treatment of every patient in-need.

Overall, there is a lack of reliable data on the current status of HCV-diagnosed patients in Spain, specially related to the changing clinical profiles of patients followed up in the specialized clinical setting. To address this gap, we conducted a national study in two phases to determine the clinical profile, management and treatment response of HCV-infected patients who are being attended by specialists in the hospital setting.

MATERIALS AND METHODS

Study Design. A nationwide, multicenter, observational, epidemiological study (named the "disHCovery" study) was designed and conducted between November 1, 2011 and May 31, 2012. The study involved two phases. The first phase was a cross-sectional analysis of the clinical features of 1,000 HCV-infected patients of any genotype (approximately 20 patients per center) followed and managed in Spanish hospitals. The second phase focused on patients infected with HCV genotype 1 (878 patients). The aim of the second phase was to compare the frequency of eight different pre-defined clinical profiles and their therapeutic management. Secondary objectives were: a) to assess differences in the outcome of patients according to different variables (age, sex, geographical site, size of the hospital, etc.), and b) to establish whether there were differences in the clinical management of patients according to the clinical profile.

The study was performed under daily practice conditions at the Hepatology outpatient clinics of 48 hospitals of the National Health Care System in 14 regions throughout Spain. The study was entirely approved by the Ethics Committee of Hos-

pital Universitari Vall d'Hebron in Barcelona, Spain. Written informed consent was obtained by all patients who participated as individuals the study.

Participants. In the first phase of the study, cross-sectional aggregated data were obtained from all patients that tested positive for HCV-specific antibodies and consecutively attended the outpatient clinics of participating hospitals over a period of 2 weeks (or during two outpatient clinic visit days in specific Hepatology Units). Data of 1,000 patients (approximately 20 patients per center) were recorded.

The second phase included patients aged 18 years or older that had been diagnosed with chronic HCV of genotype 1 and belonged to one of the following eight pre-defined clinical profile groups, depending on previous experience or not to an interferon [IFN]-based regimen: never treated, patients which have already achieved a sustained virologic response (SVR), patients currently under first-time-ever treatment, currently retreated for a second or following time, and the four groups currently untreated and previously non responders to an IFN and ribavirin based regimen (null responders, partial responders, patients who had experienced a virologic breakthrough, and relapsers). The exclusion criteria were: patients with acute hepatitis C, with any genotype different than genotype 1, coinfecting with human immunodeficiency virus (HIV) and/or hepatitis B virus (HBV), transplant recipients, previous or current inclusion in a clinical trial for treatment of chronic hepatitis C, treatment with drugs under compassionate use and cognitive decline leading to the inability to provide consent (according to the discretion of the specialist in charge).

Data collection. Data on the following variables were collected during the first phase: investigators' demographic facts, hospital characteristics, number of patients with hepatitis C followed and treated over the course of a month and percentage of patients undergoing liver biopsy and/or FibroScan. Aggregated data included number of patients, mean time from diagnosis (< 1 year, 1-5 years, 6-10 years, 11-20 years, > 20 years); age (< 20 years, 20-40 years, 41-60 years, 61-70 years, > 70 years); ethnicity; percentages of patients with detectable and undetectable HCV-RNA; frequency of the different genotypes; percentage of patients who underwent IL28B haplotype testing; fibrosis stage; status regarding liver transplantation; and patients grouped according to previous or present treatment options (never treated, currently first treatment, currently retreatment, SVR and failure to previous treatment, currently without treatment).

During the second phase, once the written informed consent was obtained, genotype 1 HCV infected patients' data were recorded at the time of a routine control (index) visit. Initially, data from the first three consecutive patients in each of the eight pre-defined clinical profile groups were collected at each centre over a period of 3 months using an electronic case report form and a web-based platform. Data were retrospectively collected from the patients' medical records or

when unavailable, during the routine index visit. The following variables were recorded: patient demographic and anthropometric data; working status; use/abuse of toxic substances; risk factors for HCV infection; comorbidities; viral load; serum levels of alanine aminotransferase (ALT); platelet count; fibrosis stage; extra-hepatic manifestations; treatment during the study period (time elapsed from the first treatment, type of treatment, duration of treatment, viral response, drug-induced severe adverse reactions, adherence [adherence rule $\geq 80/80/80$ according to patient's record]); and data related to last treatment prior to the study (type and duration of treatment, outcome, adverse events, adherence and main reason for discontinuing treatment).

General data on the investigators and centres were also recorded, including the type of hospital (academic or community), hepatitis specialized clinic visits (yes or no), investigator's years of experience, and the frequency of patient's follow-up visits.

Statistical analysis. The sample size was estimated to be able to detect a pre-defined clinical profile in 8% of the study population with an accuracy of ± 5 percentage units. Assuming an alpha risk of 0.05 (type I error) for a bilateral analysis, it was estimated that a total of 125 patients should be included per group, with incomplete or missing data no higher than 10%. Therefore, a total of 1,000 patients were required (125 per each of the eight pre-defined groups). The quantitative variables are expressed as the mean and standard deviation (SD) or median, maximum, minimum and interquartile range (IQR) (25th-75th percentile). Categorical data are expressed as frequencies and percentages. The analysis of variance (ANOVA) or the Kruskal-Wallis tests were used to make comparisons of the mean values, and chi-squared (χ^2) or the Fisher's exact tests were used to make comparisons of qualitative data, according to the normal or non-normal distribution of the variables, respectively. Statistical significance was set at $P < 0.05$. SPSS (Statistical Package for the Social Sciences) version 17.0 was used to analyse the data.

RESULTS

Phase I (data on HCV-infected patients of any genotype). A total of 48 investigators participated in the study; in one case, the data were incomplete and ultimately excluded. In terms of demographics, 66% of the investigators were men, and 70.2% had more than 15 years of practice. A total of 83% of the centres were university-affiliated hospitals, and 76.6% of the centres had specific liver units. The mean (SD) number of hepatitis C patients followed per month per investigator was 87.7 (67.1), and the mean number of patients on treatment was 32.6 (35.8). The mean frequency of follow-up visits, independently of the HCV genotype and the patient treatment experience, was every 3 months in 2.1% of cases, every 6 months in 57.4%, once a year in 31.9%, and other in 8.5%.

Forty-eight investigators provided data of between 20

Table 1 Characteristics of patients included in the first phase of the study

Data	Percentage of patients
Age, years	
< 20 to 40	18.1
41 to 60	61.4
61 to > 70	20.5
Race	
Caucasian	97.3
Asian	1
Latin American	0.6
Black African	0.5
Other	0.7
Time since diagnosis of HCV*	
< 1 year	8.3 (7.9)
1-5 years	22.6 (15.4)
6-10 years	24.1 (13.6)
11-12 years	31.4 (15.6)
> 20 years	10.9 (10.7)
Genotype*	
G1	76.6 (12.5)
1a	28.5 (17.7)
1b	69.8 (19.1)
G2	2.7 (3.5)
G3	12.3 (9.2)
G4	7.4 (7.1)
G5	0.4 (1.3)
Assessment of fibrosis (n = 962)*	
FibroScan®	38.3 (32.2)
Liver biopsy	32.2 (26.9)
Serological markers	5.3 (10.8)
Not done	24.3 (27.1)
Fibrosis stage*	
F0	9.7 (9.8)
F1	24.3 (15.5)
F2	22.7 (14.8)
F3	16.4 (10.5)
F4	26.9 (18.0)
Detectable HCV-RNA	81.4
Assessment of IL-28B haplotype	29.3

*Mean percentage (standard deviation).

and 30 patients each, with a total sum of 1,000 patients. The clinical characteristics of the patients are shown in table 1. Patient ages ranged between 41 and 60 years in 61.2% of cases, and 97.3% were Caucasian. In 34.1% of patients, time from diagnosis of HCV infection ranged between 11 and 20 years. Genotype 1 was the most frequent (76.6%), with subtype 1b in more than two third of cases (69.8%). Of the 962 patients in which data of the method used for the assessment of liver fibrosis was recorded, FibroScan was the most common (38.3%). Patients with advanced fibrosis/cirrhosis accounted for 44.5% of the cases. Furthermore, the most common stage of fibrosis was F4 (26.9% of patients) (figure 1).

The clinical profiles of the patients in relation to treatment are shown in figure 2. A mean of 35.5% of patients had failed to previous HCV treatment and were currently without treatment, 29.7% were treatment naïve (never treated), 16.6% were receiving treatment for the first time, 11.6% had SVR, and only 6.5% were currently on retreatment. Patients with failure to previous treatment and currently untreated were classified as null response (37.6%), partial response (16%), relapsers (33.2%), virologic breakthrough (2.2%), and not well typified/unavailable (9.5%). At the time of the study, 2.9% of patients were on the waiting list for liver transplantation and 0.8% were transplant recipients.

A significantly higher mean (SD) percentage of investigators with > 15 years of practice as compared with those with ≤ 15 years performed IL28B haplotype testing (35.8 [29.4] vs 12.1 [17.4], $P < 0.05$). The results of other bivariate comparisons were not significant.

Phase II (data on genotype 1 HCV-infected patients).

Data of 899 patients with genotype 1 HCV infection were collected, with 21 patients (2.3%) excluded because they did not fulfil the inclusion criteria (11 patients) or because the data were incomplete (10 patients). Therefore, 878 patients qualified for the second phase analysis.

Salient clinical features are shown in table 2. The mean (SD) age of patients was 51.4 (10.7) years, 98.7% were Caucasian and 55.4% were men. The mean (SD) body mass index was 26.2 (3.9) kg/m. The most frequent risk factors for acquiring HCV infection were blood transfusion or organ transplantation (before 1990) in 24% of patients and current or past intravenous drug use in 13.4%. Of the 59 patients with extrahepatic manifestations, the most common were thyroid disease in 35.6% of cases, mixed cryoglobulinemia in 23.7%, and auto-antibodies in 16.9%.

The distribution of patients according to the eight pre-defined clinical profiles groups is shown in figure 3. Patients treated previously without achieving SVR and not receiving current anti-HCV treatment accounted for 50.8% of the cases; patients with SVR accounted for 14.5%; and treatment-naïve (never treated) patients accounted for 15.9%. Excluding patients currently under treatment for the first time (12.6%) and those currently being retreated (6.2%), the remaining 713 (81.2%) patients were currently not receiving

Table 2		Salient clinical characteristics of 878 patients with chronic genotype 1 hepatitis C included in the second phase of the study
Variables	No. patients (%)	
Sex		
Male	486 (55.4)	
Female	392 (44.6)	
Age, years, mean (SD)	51.4 (10.7)	
Ethnicity		
Caucasian	867 (98.7)	
Black	5 (0.6)	
Asiatic	1 (0.1)	
Other	5 (0.6)	
Body mass index (BMI), kg/m ² , mean (SD)	26.2 (3.9)	
Working status		
Active worker	497 (54.6)	
Sick leave	44 (5.0)	
Not working	355 (40.4)	
Smoking habit		
Never smoker	507 (57.7)	
Ex-smoker	148 (16.9)	
Current smoker	223 (25.4)	
Alcohol consumption		
Never alcohol use	705 (80.3)	
Ex-consumer	125 (14.2)	
Current consumer	48 (5.5)	
Drug abuse		
Never consumed	758 (86.3)	
Ex-user (intravenous/nasal routes)	111 (12.6)	
Current user (intravenous/nasal routes)	9 (1.0)	

Table 2		Salient clinical characteristics of 878 patients with chronic genotype 1 hepatitis C included in the second phase of the study (cont.)
Variables	No. patients (%)	
Time since diagnosis, years (n = 858)		
< 1	26 (3.0)	
1-5	161 (18.8)	
6-10	164 (19.1)	
11-20	338 (39.4)	
> 20	169 (19.7)	
Risk factors		
Blood transfusion or organ recipients (prior to 1990)	211 (24.0)	
Intravenous drug use	118 (13.4)	
Hospital admission/invasive diagnostic procedures/surgery	81 (9.2)	
Tattoos/piercing	29 (3.3)	
Sexual transmission	20 (2.3)	
Vertical transmission	14 (1.6)	
Other	44 (5.0)	
Unknown	361 (41.1)	
Fibrosis stage (n = 671)		
F0-F1	232 (34.6)	
F2	144 (21.5)	
F3-F4	295 (44)	
Other clinical characteristics		
HCV-RNA log ¹⁰ , mean (SD)*	5.7 (1.4)	
Serum ALT \geq 45 IU/L*	504 (57.4)	
Platelet count, cells/mm ³ , mean (SD)*	180,691.3 (74,277.8)	
Presence of comorbid conditions	286 (32.6)	
Extrahepatic clinical manifestations	59 (6.7)	

*Last available value; data expressed as frequencies and percentages in parenthesis unless otherwise stated.

any type of therapy. Reasons for not being currently treated included waiting for new anti-HCV drugs (41.8%), previous SVR (17.8%), lack of efficacy of current regimens (9.5%), patient refusal (6.2%) and absent or mild liver damage (6.2%) (table 3).

In terms of previous treatment, 95.4% of patients had received double therapy (pegylated interferon= [PEG-IFN] alpha-2a and ribavirin in 62.5% of patients and PEG-IFN alpha-2b and ribavirin in 37.5%). The duration of previous treatment had been 48 weeks in 85.5% of cases. An adherence rate of 90.4% was achieved (adherence rule \geq 80/80/80) according to patient records. Treatment-related severe adverse events were recorded in 12 patients (anemia in 8, endocrine-metabolic disorders in 2, rash in 1 and neuropsychiatric disorders in 1). In terms of current treatment in 165 patients (first treatment

or retreatment), 75.8% of patients were treated with double therapy (PEG-IFN α -2a and ribavirin in 79.2%, PEG-IFN α -2b and ribavirin in 20.8%), in 15.8% of them the proposed duration was 72 weeks.=

There were significant differences among the different clinical profiles. Patients currently undergoing treatment for the first time were younger ($P < 0.001$) and showed a shorter interval since the diagnosis ($P < 0.05$) as compared with the remaining groups. In addition, the distribution of fibrosis stage varied significantly among the eight pre-defined groups ($P < 0.005$), with the highest percentage of patients with F0/F1 in the never-treated patients group and the highest percentage of F4 in the group of patients currently undergoing retreatment.

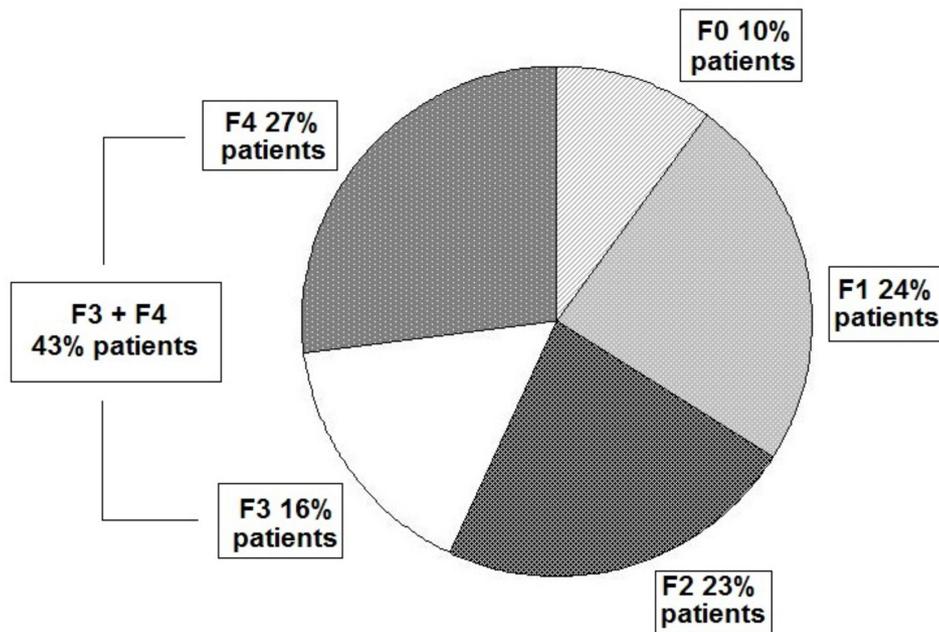


Figure 1 Distribution of stages of fibrosis (n = 726).

DISCUSSION

The current HCV treatment scenario is complex, with some recently introduced direct acting antivirals (DAA) and new promising drugs and combinations in the treatment's pipeline expected to be available soon⁹. Therefore, there is a vast need of data on patients' clinical profiles and previous treatment responses in order to address the need of treatment of these individuals, a great majority of whom are not yet cured or even have not yet been treated with previously available options. Specifically, there is a lack of data on different genotypes prevalence, current fibrosis stages and previous treatment responses, even in the group of patients already followed in the Hepatology Units throughout the National Health System.

Ideally, a national epidemiological study should have been developed, especially considering the high percentage of HCV-infected people who remain unaware of the infection. Due to budget and time limitations, it was decided to start with a study focused on patients already diagnosed and followed in Hepatology Units throughout Spain, presumably those patients with a more peremptory need for treatment.

The present findings demonstrate that most patients with chronic hepatitis C attended in the hospital setting in Spain, were infected with HCV genotype 1 infection (76.6%), but also significant groups are infected by genotype 3 (12.3%) and 4 (7.4%). The patients showed more frequently advanced hepatic fibrosis/cirrhosis, and failure to previous IFN and ribavirin treatment/s (with a majority of patients being null responders or relapsers after initial HCV therapy).

The subset of patients with genotype 1 HCV infection was characterized by an advanced fibrosis or cirrhosis (44%) and made mostly by currently untreated patients (treatment-naïve or with previous failure to anti-HCV therapy) waiting for new treatment options at the time of the data collection.

The high prevalence of genotype 1, particularly genotype 1b, found in our study is consistent with previously reported data in Spain. In a study of the prevalence of hepatitis C virus genotypes in a Spanish liver transplant unit, the overall distribution of genotypes in 108 patients was 1b in 86.1%, 1a in 7.4%, genotype 3 in 3.7%, genotype 4 in 1.9%, and genotype 2 in 0.9%¹⁰. Also, it has been shown that among HIV/HCV coinfecting patients, those with genotype 4 the efficacy of PEG-IFN with ribavirin was significantly higher than in those with genotype 1¹¹.

A study of the prevalence of hepatitis C virus genotypes in Spain during a nine-year period (1996-2004) indicated that two separate epidemics of HCV seem to have occurred in Spain over the last 30 years. The former one involved the spread of HCV genotypes 1a and 3. The second was more recent, and involved the spread of genotype 4¹². In our study, genotypes 3 (12.3%) and 4 (7.4%) were the most frequent after genotype 1. Additionally, findings of the present study should be interpreted taking into account some other limitations of the study especially those related to the retrospective design regarding incomplete data collection and the impossibility to establish causality relationships. However, the epidemiological characteristics of the study and the inclusion of a large study population of patients with hepatitis C recruited in a large number of

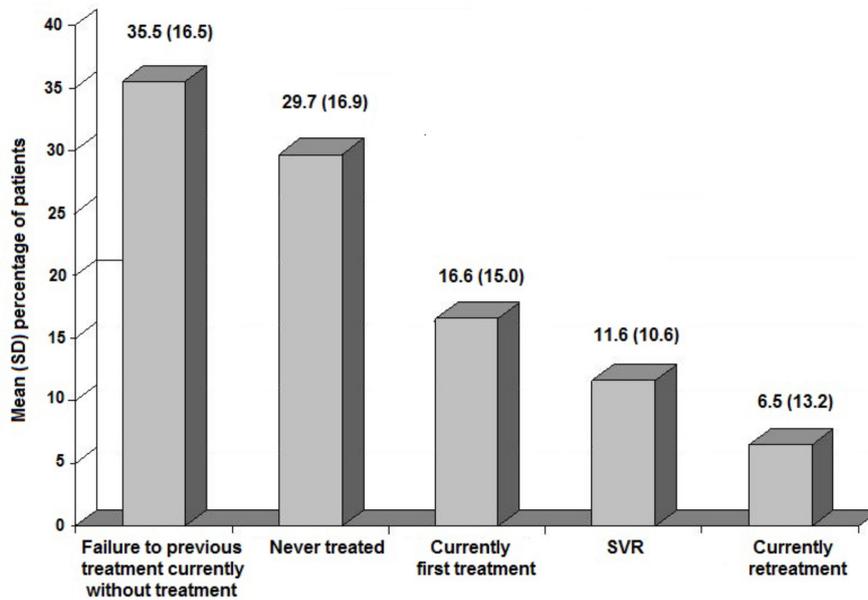


Figure 2 Distribution of mean (SD) of the percentages of patients who participated in the first phase (any genotype) of the study according to treatment.

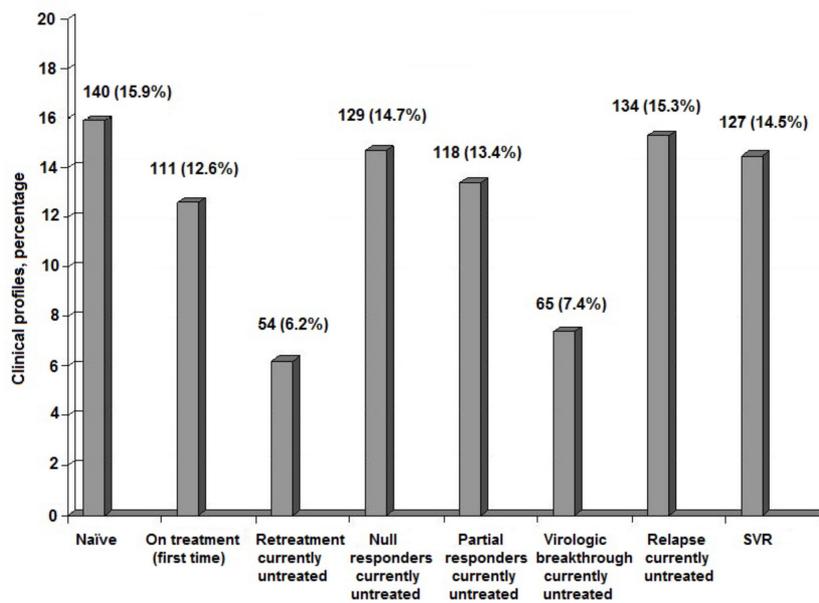


Figure 3 Number of patients and percentages of the eight pre-defined clinical profiles in patients with genotype 1 HCV infection included in the second phase of the study (HCV genotype 1 patients) (SVR: sustained virologic response).

Table 3 Reasons for not being currently treated with HCV drugs in 713 patients

Reason	No. patients (%)
Waiting for new HCV drugs	298 (41.8)
SVR achieved	127 (17.8)
Lack of efficacy of current treatment regimens	68 (9.5)
Patient's refusal	44 (6.2)
Absence or mild liver damage (F0/F1)	44 (6.2)
Age > 65 years	29 (3.6)
Contraindication	19 (2.7)
Comorbidities	14 (2.0)
New patient (first visit)	13 (1.8)
Poor motivation/poor adherence	6 (0.8)
Normal serum aminotransferase levels	3 (0.4)
Low viral load	1 (0.1)
Miscellaneous or other	50 (7.0)

SVR: sustained virologic response.

hospitals throughout the country ensures representativeness of patients and the external validity of the study.

In summary, patients with genotype 1 (76.6%) chronic HCV, predominately 1b (69.8% out of genotype 1), seem to be the most prevalent group of HCV-infected individuals in Spain, with other significant groups infected by genotype 3 (12.3%) and 4 (7.4%). Advanced fibrosis or cirrhosis is most frequent in this patient group, which mainly includes individuals in need for treatment (never treated, with relapse or unresponsiveness to IFN-ribavirin combination treatments). The main reason for not being currently treated is to be waiting for new anti-HCV drugs and the lack of efficacy of available regimens at the time of the study.

Footnotes:

- Institutional Review Board statement: the disHCovery study was entirely approved by the Ethics Committee of Hospital Universitari Vall d'Hebron in Barcelona, Spain.
- Informed consent statement: written informed consent was obtained by all patients who participated as individuals the study.
- Clinical trial registration statement: The trial is not an interventional study, so following the definitions of ClinicalTrials.gov, the study does not qualify as a clinical trial for registration.
- Institutional Animal Care and Use Committee statements: The trial does not include procedures involving animals.

- Biostatistics statement: The statistical methods of this study were reviewed by a biostatistician of the CRO Dynamic Solutions.
- Conflict-of-interest statement: M Buti declares having participated as an advisory board member for Janssen, MSD and Gilead. A Franco is a Janssen employee. I Carmona, JJ Sánchez-Ruano, A Sansó, M Berenguer, L García-Buey, M Hernández-Guerra, and RM Morillas declare not having any conflict of interests. F Ledesma is a Janssen employee. R Esteban declares having participated as an advisory board member for Janssen, MSD and Gilead and Abbvie.
- Data sharing statement: No additional data are available for the study.

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