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Treatment indications in chronic hepatitis C authorized in Castilla y León (Spain) during the study period.

- December 1, 2014 to March 31, 2015: 1) Patients with fibrosis stage F3-F4. 2) Patients with any fibrosis stage if meet any of these requirements: a) patients with extrahepatic manifestations of the infection, b) patients with high viral loado and high level of transmission, depending on the social/professional situation, c) young women with desire to procreate.
- April 1, 2015 to August 30, 2015: patients with characteristics described above and also patients with fibrosis stage F2, even though it is considered that its treatment is less imperative*

Drugs available and authorized in Castilla y León (Spain) to treat chronic hepatitis C during the study period.

- December 1, 2014 to the end of period of inclusion: simeprevir (SMV), sofosbuvir (SOF) and ribavirina (RBV).
- January 27, 2015 to the end of period of inclusion: daclatasvir (DCV).
- April 1, 2015 to the end of period of inclusion: ledipasvir (LDV), ombitasvir (OBV)/paritaprevir (PTV)/ritonavir (r), dasabuvir (DSV).
- *In May 21, 2015 appeared in Spain a National Hepatitis C Plan developed by the Spanish Ministry of Health, that was followed by all the physicians that participate in the study (available in: http://www.msssi.gob.es/ciudadanos/enfLesiones/enfTransmisibles/docs/plan_estrategico_hepatitis_C.pdf)

Table 2. Supplementary Material. Continuous and categorical variables evaluated.

BMI, body mass index; PEG, pegylated interferon; PIs, protease inhibitors; ALT, alanine aminotransferase; SMV, simeprevir; SOF, sofosbuvir; DCV, daclatasvir; LDV, ledipasvir; OMV, ombitasvir,; PTV/r, paritraprevir / ritonavir; DSV, dasabuvir; RBV, ribavirin; CT, clinical trial; SVR, sustained viral response; RVR, rapid viral response; SAE, severe adverse effects; AE, adverse effects.

IL28B genotype, interleukin-28B genotype (rs12979860, LightMix Kit rs12979860; Roche Molecular Systems, Nutley, New Jersey, USA).

Liver stiffness (kPa) was measured by transient elastography (FibroScan®; Echosens, Paris, France) anytime in 24 weeks before starting treatment. The degree of fibrosis evidenced by LS was stratified using the METAVIR scale with the following cutoffs: F0–F1 (< 7.2 kPa), F2 (7.2–9.4 kPa), F3 (9.5–12.5 kPa), and F4 (>12.5 kPa).

Child-Pugh score and Model for End-Stage Liver Disease (MELD) score was calculated in patients with cirrhosis.

Categorical variables	**Continuous variables**
Age (>65 years)	Age
Sex (female/male)	BMI, kg/m^2
BMI, kg/m^2 (<30/ ≥ 30)	Baseline HCV RNA, log_{10} IU/mL
IL28B genotype (CC/CT/TT)	Transient elastography, kPa
HCV genotype (1/2/3/4)	Hemoglobin level, g/dL
HCV subgenotype (1a/1b/1)	Platelets, mm^3
Baseline HCV RNA, log_{10} IU/mL (≤800.000/>800.000)	INR
HCV antiviral treatment history (Yes/No)	Creatinine, mg/dL
HCV antiviral treatment history (No/Non-responders/Relapsers/Unknown)	Bilirubin, mg/dL

Categorical variables	**Continuous variables**
HCV antiviral treatment history (No/Previous therapy with Peg-IFN + RBV/Previous therapy with PIs)	ALT, IU/L
Transient elastography, kPa (<20/≥20)	Albumin, g/dL
Transient elastography, kPa (<25/≥25)	MELD score
Fibrosis stage (F0-1/F2/F3/F4)	Child−Pugh Score
Cirrhosis (yes/no)	
MELD score (<12/≥ 12)	
Child−Pugh Score (A/B/C)	
Platelets, /mm³ (<100,000/≥100,000)	
Bilirubin, mg/dL (≤1/>1)	
Albumin, g/dL (< 3.5/≥3.5)	
Treatment at University Hospital (yes/no)	
CT (met/unmet)	
Treatment prescribed (SMV+SOF/SMV+DCV/SOF+DCV/SOF/OMV+PTV/r/OMV+PTV/r+DSV/SOF+LDV)	
Treatment prescribed SOF (yes/no)	
Treatment duration, weeks: (8/12/24)	
RBV (yes/no)	
RVR (yes/no)	
SVR (yes/no)	

Categorical variables	Continuous variables
AE (yes/no)	
SAE (yes/no)	
Treatment discontinuation (yes/no)	
Anemia (yes/no)	
Ribavirin dose reduction (Yes/No)	
Transfusion (yes/no)	
Liver decompensation (yes/no)	

Table 3. Supplementary Material. Sustained virological response by continuous and categorical variables evaluated.

Continuous variables reported as median (range). Categorical variables reported as n (%).

SVR, Sustained virological response; BMI, body mass index; PEG, pegylated interferon; RBV,ribavirin; PIs, protease inhibitors; ALT, alanine aminotransferase; CT, clinical trial; SMV, simeprevir; SOF, sofosbuvir; DCV, daclatasvir; LDV, ledipasvir; OMV, ombitasvir; PTV/r, paritraprevir / ritonavir; DSV, dasabuvir; AE, adverse events; SAE, serious adverse events.

	SVR		
	Yes (n=437)	**No (n=25)**	**p=**
Sex			0.164
female	146 (96.7)	5 (3.3)	
male	291 (93.6)	20 (6.4)	

Age, years	54 (15-87)	52 (33-84)	0.241
≤ 65	338 (93.9)	22 (6.1)	0.212
> 65	99 (97.1)	3 (2.9)	
BMI, kg/m^2	26 (17-47)	26 (20-46)	0.414
< 30	291 (95.4)	14 (4.6)	0.525
≥ 30	59 (93.7)	4 (6.3)	
IL28B genotype			-
CC	76 (95.0)	4 (5.0)	
CT	220 (95.2)	11 (4.8)	
TT	51 (91.1)	5 (8.9)	
IL28B genotype			1.000
CC	76 (95.0)	4 (5.0)	
CT+TT	271 (94.4)	16 (5.6)	
HCV genotype			-
1	342 (94.5)	20 (5.5)	
2	11 (100)	0 (0)	
3	42 (93.3)	3 (6.7)	
4	42 (95.5)	2 (4.5)	
HCV genotype			0.725
3	42 (93.3)	3 (6.7)	
1+2+4	395 (94.7)	22 (5.3)	
HCV subtype			0.129
1a	108 (97.3)	3 (2.7)	
1b	225 (93.4)	16 (6.6)	
HCV antiviral treatment history			0.978
No	176 (94.6)	10 (5.4)	
Yes	261 (94.6)	15 (5.4)	

HCV antiviral treatment history Null + partial Relapser	 197 (93.4) 63 (98.4)	 14 (6.6) 1 (1.6)	 0.205
HCV antiviral treatment history Null + partial Naïve + Relapsers	 197 (93.4) 238 (95.6)	 14 (6.6) 11 (4.8)	0.296
HCV antiviral treatment history Naïve Previous therapy with Peg-IFN + RBV Previous therapy with PIs	 176 (94.6) 176 (94.6) 85 (94.4)	 10 (5.4) 10 (5.4) 5 (5.6)	-
Baseline HCV RNA, log_{10} IU/mL	5.17 (2.98-7.62)	5.99 (5.24-7.80)	0.505
Baseline HCV RNA, log_{10} IU/mL ≤800.000 >800.000	 144 (92.9) 293 (95.4)	 11 (7.1) 14 (4.6)	0.255
Transient elastography, kPa	13.1 (2.8-75)	20.9 (8-47)	0.003
Transient elastography, kPa < 20 ≥20	 302 (96.5) 110 (90.2)	 11 (3.5) 12 (9.8)	0.008
Transient elastography, kPa	338 (96.3) 74 (88.1)	13 (3.7) 10 (11.9)	0.006

< 25 ≥25			
Fibrosis stage F0-1	26 (100.0)	0 (0.0)	-
F2	97 (97.0)	3 (3.0)	
F3	73 (98.6)	1 (1.4)	
F4	241 (92.0)	21 (8.0)	
Cirrhosis No Yes	 196 (98) 241 (92)	 4 (2.0) 21 (8.0)	0.005
Hemoglobin level, g/dL	15(8.0-19.5)	15 (10.1-17.7)	0.620
Platelets, /mm³	158,000 (23,000-457,000)	113000 (40000-418000)	0.056
Platelets, /mm³ <100,000 ≥100,000	 95 (89.6) 144 (92.9)	 11 (10.4) 14 (4.1)	0.014
INR	1.05 (0.7-2.9)	1.1 (0.88-1.3)	0.896
Creatinine, mg/dL	0.81 (0.3-2.3)	0.83 (0.49-2.3)	0.423
ALT, IU/L	64 (9 ; 436)	75 (17-236)	0.798
Bilirubin, mg/dL	0.82 (0.2-5.78)	1.0 (0.5-5.0)	0.121
Bilirubin, mg/dL >1 ≤1	 85 (90.4) 139 (93.3)	 9 (9.6) 10 (6.7)	0.418
Albumin, g/dL	4.23(2.16-5.3)	4 (3.43-4.65)	0.040

Albumin, g/dL			1.000
<3.5	23 (92.0)	2 (8.0)	
≥3.5	200 (92.2)	17 (7.8)	
Child-Pugh score	5 (5-14)	5 (5-13)	0.301
Child-Pugh score			0.265
A	167 (92.8)	13 (7.2)	
B+C	25 (86.2)	4 (13.8)	
MELD score	7 (6-29)	7.5 (6-17)	0.843
MELD score			1.000
<12	188 (92.2)	16 (7.8)	
≥12	23 (92.0)	2 (8.0)	
Treatment at University Hospital			1.000
No	64 (95.5)	3 (4.5)	
Yes	373 (94.4)	22 (5.6)	
CT			0.049
unmet	159 (91.9)	14 (8.1)	
met	278 (96.2)	11 (3.8)	
Treatment prescribed			-
SMV and SOF	157 (93.5)	11 (6.5)	
SMV and DCV	7 (100)	0 (0)	
SOF and DCV	54 (94.7)	3 (5.3)	
SOF	11 (100)	0 (0)	
OMVand PTV/r	12 (92.3)	1 (7.7)	
OMV and PTV/r+DSV	86 (94.5)	5 (5.5)	
SOF and LDV	110 (95.7)	5 (4.3)	
Treatment prescribed	105 (94.6)	6 (5.4)	0.998
No SOF	332 (94.6)	19 (5.4)	

SOF			
Treatment duration, weeks 8 + 12 24	395 (94.3) 42 (97.7)	24 (5.7) 1 (2.3)	0.496
RBV No Yes	251 (95.1) 186 (93.9)	13 (4.9) 12 (6.1)	0.593
RVR No Yes	111 (89.5) 321 (96.4)	13 (10.5) 12 (3.6)	0.004
AE No Yes	239 (94.1) 198 (95.2)	15 (5.9) 10 (4.8)	0.682
SAE No Yes	427 (94.7) 10 (90.9)	24 (5.3) 1 (9.1)	0.461
Treatment discontinuation No Yes	434 (94.8) 3 (75.0)	24 (5.2) 1 (25.0)	0.200
Anemia No Yes	372 (94.4) 49 (94.2)	22 (5.6) 3 (5.8)	1.000
RBV dose reduction No Yes	169 (95.5) 17 (81.0)	8 (4.5) 4 (19.0)	0.027

Transfusion No Yes	 204 (94.4) 4 (100)	 12 (5.6) 0 (0)	1.000
Liver decompensation No Yes	 430 (94.5) 7 (100)	 25 (5.5) 0 (0)	1.000

Table 4. Supplementary Material. Sustained virological response rates (confidence interval 95%) according to HCV genotype and different variables.

GT, genotype; SVR, sustained virological response; BMI, body mass index; PEG, pegylated interferon; RBV, ribavirin; PIs, protease inhibitors; ALT, alanine aminotransferase; SMV, simeprevir; SOF, sofosbuvir; DCV, daclatasvir; LDV, ledipasvir; OMV, ombitasvir; PTV/r, paritraprevir / ritonavir; DSV, dasabuvir; RVR, rapid virological response; CT, clinical trial.

SVR	n	All patients	GT 1	GT 2	GT 3	GT 4
n		462	362	11	45	44
All patients	462	94.6 (92.5-96.7)	94.5 (92.1-96.8)	100.0 (100.0-100.0)	93.3 (86.0-100.6)	95.5 (89.3-101.6)
SVR in the following subgroups						
Sex	462					
Male	311	93.6 (90.8-96.3)	93.5 (90.3-96.7)	100.0 (100.0-100.0)	91.2 (81.6-100.7)	94.9 (87.9-101.8)
Female	151	96.7 (93.8-	96.2 (92.9-	100.0 (100.0-	100.0	100.0

		99.5)	99.5)	100.0)	(100.0-100.0)	(100.0-100.0)
Age	462					
<65 years	360	93.9 (91.4-96.4)	93.5 (90.5-96.5)	100.0 (100.0-100.0)	93.3 (86.0-100.6)	95.5 (89.3-101.6)
≥65 years	102	97.1 (93.8-100.3)	97.0 (93.7-100.3)	100.0 (100.0-100.0)		
BMI	368					
<30	305	95.4 (93.1-97.8)	95.7 (93.2-98.3)	100.0 (100.0-100.0)	93.8 (85.4-102.1)	93.9 (85.8-102.1)
≥30	63	93.7 (87.6-99.7)	94.0 (87.4-100.6)	100.0 (100.0-100.0)	83.3 (53.5-113.2)	100.0 (100.0-100.0)
IL28B genotype	447					
CC	80	95.0 (90.2-99.8)	94.2 (87.9-100.6)	100.0 (100.0-100.0)	94.1 (82.9-105.3)	100.0 (100.0-100.0)
Non-CC	287	94.4 (91.8-97.1)	94.8 (92.0-97.5)	100.0 (100.0-100.0)	92.9 (79.4-106.3)	90.5 (77.9-103.0)
HCV subtype	354					
1a	113	97.3 (94.4-100.3)	97.3 (94.3-100.3)			
1b	241	93.4 (90.2-96.5)	93.4 (90.2-96.5)			
Baseline HCV RNA. $\log_{10}$	462					

IU/mL						
<800.000 IU/ml	155	92.9 (88.9-96.9)	93.4 (89.0-97.8)	100.0 (100.0-100.0)	87.5 (71.3-103.7)	92.3 (77.8-106.8)
≥800.000 IU/ml	307	95.4 (93.1-97.8)	95.0 (92.3-97.8)	100.0 (100.0-100.0)	96.6 (89.9-103.2)	96.8 (90.6-103.0)
HCV antiviral treatment history	460					
Naïve	185	94.6 (91.3-97.9)	95.0 (91.4-98.6)	100.0 (100.0-100.0)	92.3 (82.1-102.6)	91.7 (76.0-107.3)
Non-responders	211	93.4 (90.0-96.7)	92.9 (89.0-96.8)	100.0 (100.0-100.0)	92.9 (79.4-106.3)	96.2 (88.8-103.5)
Relapsers	64	98.4 (95.4-101.5)	98.0 (94.2-101.8)	100.0 (100.0-100.0)	100.0 (100.0-100.0)	100.0 (100.0-100.0)
Previous therapy with Peg-IFN + RBV	186	94.6 (91.4-97.9)	94.2 (90.3-98.1)	100.0 (100.0-100.0)	94.4 (83.9-105.0)	96.2 (88.8-103.5)
Previous therapy with PIs	91	94.5 (89.8-99.2)	94.0 (89.0-99.1)		100.0 (100.0-100.0)	100.0 (100.0-100.0)
Fibrosis stage						
F0–1	26	100.0 (100.0-100.0)	100.0 (100.0-100.0)	100.0 (100.0-100.0)		100.0 (100.0-100.0)
F2	100	97.0 (93.7-100.3)	96.1 (91.8-100.4)	100.0 (100.0-100.0)	100.0 (100.0-	100.0 (100.0-

					100.0)	100.0)
F3	74	98.6 (96.0-101.3)	100.0 (100.0-100.0)	100.0 (100.0-100.0)	100.0 (100.0-100.0)	83.3 (53.5-113.2)
F4	262	92.0 (88.7-95.3)	91.6 (87.8-95.4)	100.0 (100.0-100.0)	90.3 (79.9-100.7)	95.8 (87.8-103.8)
Transient elastography. kPa.	435					
< 20	313	96.5 (94.4-98.5)	96.5 (94.2-98.7)	100.0 (100.0-100.0)	95.5 (86.8-104.2)	96.6 (89.9-103.2)
≥ 20	122	90.2 (84.9-95.4)	89.7 (83.3-96.1)	100.0 (100.0-100.0)	88.2 (72.9-103.6)	92.9 (79.4-106.3)
< 25	351	96.3 (94.3-98.3)	96.4 (94.3-98.6)	100.0 (100.0-100.0)	96.4 (89.6-103.3)	94.3 (86.6-102.0)
≥ 25	84	88.1 (81.2-95.0)	87.1 (78.8-95.4)	100.0 (100.0-100.0)	81.8 (59.0-104.6)	100.0 (100.0-100.0)
Cirrhosis	462					
No	200	98.0 (96.1-99.9)	98.1 (96.0-100.2)	100.0 (100.0-100.0)	100.0 (100.0-100.0)	95.0 (85.4-104.6)

Yes	262	92.0 (88.7-95.3)	91.6 (87.8-95.4)	100.0 (100.0-100.0)	90.3 (79.9-100.7)	95.8 (87.8-103.8)
Child−Pugh Score	209					
A	180	92.8 (89.0-96.6)	92.8 (88.5-97.1)	100.0 (100.0-100.0)	90.0 (76.9-103.1)	94.7 (84.7-104.8)
B	22	86.4 (72.0-100.7)	81.8 (59.0-104.6)	100.0 (100.0-100.0)	85.7 (59.8-111.6)	100.0 (100.0-100.0)
C	7	85.7 (59.8-111.6)	85.7 (59.8-111.6)			
MELD score	229					
<12	204	92.2 (88.5-95.8)	92.3 (88.1-96.5)	100.0 (100.0-100.0)	87.5 (74.3-100.7)	95.0 (85.4-104.6)
≥12	25	92.0 (81.4-102.6)	88.2 (72.9-103.6)		100.0 (100.0-100.0)	100.0 (100.0-100.0)
Platelets. /mm³	446					
<100.000	106	89.6 (83.8-95.4)	89.2 (82.5-95.8)	100.0 (100.0-100.0)	88.2 (72.9-103.6)	100.0 (100.0-100.0)
≥100.000	340	95.9 (93.8-98.0)	95.8 (93.4-98.3)	100.0 (100.0-100.0)	96.4 (89.6-103.3)	94.6 (87.3-101.9)
Albumin g/dL	242					
<3.5	25	92.0 (81.4-	94.4 (83.9-		83.3 (53.5-	100.0

		102.6)	105.0)		113.2)	(100.0-100.0)
≥3.5	217	92.2 (88.6-95.7)	91.5 (87.3-95.8)	100.0 (100.0-100.0)	92.0 (81.4-102.6)	95.5 (86.8-104.2)
Treatment prescribed	462					
SMV and SOF	168	93.5 (89.7-97.2)	93.3 (89.3-97.3)			94.7 (84.7-104.8)
SMV and DCV	7	100.0 (100.0-100.0)	100.0 (100.0-100.0)			
SOF and DCV	57	94.7 (88.9-100.5)	100.0 (100.0-100.0)	100.0 (100.0-100.0)	91.9 (83.1-100.7)	
SOF	11	100.0 (100.0-100.0)		100.0 (100.0-100.0)	100.0 (100.0-100.0)	100.0 (100.0-100.0)
OMV and PTV/r	13	92.3 (77.8-106.8)				92.3 (77.8-106.8)
OMV. PTV/r. and DSV	91	94.5 (89.8-99.2)	94.5 (89.8-99.2)			
SOF and LDV	115	95.7 (91.9-99.4)	95.0 (90.7-99.3)	100.0 (100.0-100.0)	100.0 (100.0-100.0)	100.0 (100.0-100.0)
with RBV	198	93.9 (90.6-97.3)	94.7 (90.9-98.5)	100.0 (100.0-100.0)	90.6 (80.5-100.7)	92.6 (82.7-102.5)

without RBV	264	95.1 (92.5-97.7)	94.3 (91.4-97.3)	100.0 (100.0-100.0)	100.0 (100.0-100.0)	100.0 (100.0-100.0)
Treatment duration	462					
8 weeks	12	91.7 (76.0-107.3)	91.7 (76.0-107.3)			
12 weeks	407	94.3 (92.1-96.6)	94.3 (91.8-96.8)	100.0 (100.0-100.0)	93.5 (84.9-102.2)	94.9 (87.9-101.8)
24 weeks	43	97.7 (93.2-102.2)	100.0 (100.0-100.0)	100.0 (100.0-100.0)	92.9 (79.4-106.3)	100.0 (100.0-100.0)
RBV dose reduction	198					
No	177	95.5 (92.4-98.5)	95.8 (92.2-99.4)	100.0 (100.0-100.0)	95.8 (87.8-103.8)	92.6 (82.7-102.5)
Yes	21	81.0 (64.2-97.7)	84.6 (65.0-104.2)		75.0 (45.0-105.0)	
Treatment at University Hospital	395	94.4 (92.2-96.7)	94.4 (91.9-97.0)	100.0 (100.0-100.0)	92.9 (85.1-100.6)	94.6 (87.3-101.9)
Treatment at non-University Hospital	67	95.5 (90.6-100.5)	94.7 (88.9-100.5)		100.0 (100.0-100.0)	100.0 (100.0-100.0)
RVR	457					
No	124	89.5 (84.1-	88.7 (82.3-	100.0 (100.0-	92.9 (79.4-	87.5 (64.6-

		94.9)	95.0)	100.0)	106.3)	110.4)
Yes	333	96.4 (94.4-98.4)	96.6 (94.4-98.8)	100.0 (100.0-100.0)	93.3 (84.4-102.3)	97.1 (91.6-102.7)
CT-met	462					
Yes	289	96.2 (94.0-98.4)	96.4 (93.9-98.8)	100.0 (100.0-100.0)	93.3 (84.4-102.3)	97.0 (91.1-102.8)
No	173	91.9 (87.8-96.0)	91.5 (87.0-96.1)	100.0 (100.0-100.0)	93.3 (80.7-106.0)	90.9 (73.9-107.9)