A multicentre, observational study on demographic and disease characteristics of patients seeking care for chronic hepatitis C in Belgium in 2016

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Abstract

***Background and Study Aims* : Direct-acting antivirals provide interferon-free treatments for chronic hepatitis C (CHC) virus infection. In Belgium, in 2016, access to these agents was limited to patients with advanced liver fibrosis stages F3 and F4. This study is the first to describe Belgium's patient population ineligible for interferon-free treatment.**

***Patients and Methods* : This was an observational, cross-sectional, multicentre study that enrolled adult patients with CHC ineligible for interferon-free treatment. Patient data recorded at a single visit included demographic data, disease characteristics, comorbidities, co-medications, treatment status, and laboratory data.**

***Results* : Three hundred and three patients from 16 centres in Belgium were included in the statistical analysis. On average, patients were aged 53.5 years and 50.2% were women ; 94.1% had health insurance and 99.0% resided in Belgium. The current hepatitis C virus (HCV) infection was the first infection for 96.0% of patients and the mean time since infection was 20.0 years. Liver fibrosis stage was F0 for 23.7%, F0/F1 or F1 for 38.3%, F1/F2 or F2 for 25.8%, F3 for 7.1%, and F4 for 5.1% of patients ; 28.4% of patients were CHC treatment-experienced. The main reason for ineligibility for interferon-free treatment was lack of reimbursement (84.8%). Other reasons included no treatment urgency or medical decision to wait (27.1%), waiting for future treatment option (8.3%), and no social insurance coverage (3.6%).**

***Conclusions* : This study provides recent data on the CHC patient population and disease characteristics in Belgium that could help medical communities and government agencies manage CHC disease burden.** (Acta gastroenterol. belg., **2019**, 82, **43-52**).

Key words : Belgium, chronic hepatitis C, direct antiviral agent, interferon-free regimen, observational.

1. Introduction

Hepatitis C virus (HCV) infection is a public health problem throughout the world. It is estimated that between 64 and 103 million individuals are living with chronic hepatitis C (CHC) infection worldwide (1).

In 2014, the European Medicines Agency approved new direct-acting antiviral (DAA) agents for the treatment of patients with CHC infection, to be used with or without ribavirin, which allows patients to be treated without interferon (IFN). However, access to DAA regimens in some countries, including Belgium, was limited in 2016 to patients with HCV infection with liver fibrosis stages 3 (F3) and 4 (F4).

Data describing the demographic and disease characteristics of patients seeking care for HCV infection in Belgium are scarce. Most of the available data come from post-marketing observational studies (2-6) with IFN-based therapies, hence only reflecting the demographic and basic clinical characteristics of those patients who were eligible for this specific therapy. Only one Belgian study described the demographic and basic clinical characteristics of patients seeking care for HCV infection without inclusion bias (7). However, the study results are outdated, as patient recruitment ran from November 2003 until November 2004 and the natural progression of the disease and the arrival of new-generation DAAs have impacted the patient population under care (8).

Data describing the demographic and disease characteristics of patients with HCV infection who do not have access to treatment, especially to INF-free regimens are non-existent in Belgium. This observational epidemiologic study was designed to describe the demographic, disease, and treatment characteristics of patients with CHC infection in Belgium in 2016 who were not eligible for treatment with IFN-free regimens.

2. Patients and Methods

2.1. Study Design and Patients

This was an observational, cross-sectional, multicentre study of patients with CHC infection in Belgium. The study took place between February 9, 2016, and June 1, 2016, in 16 active study centres throughout Belgium, providing a geographical range of study centres designed to capture variability between regions.

Eligible patients were enrolled consecutively at participating clinical centres and included men or women 18 years or older who were diagnosed with CHC (irrespective of co-infections, HCV genotypes, and previous treatment for CHC) and were not eligible for treatment with currently approved IFN-free regimens. Patients with acute HCV infection or patients

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participating in a concurrent interventional clinical trial were excluded.

Patient data were collected during a single routine visit. For each patient, participating physicians were asked to fill in a structured case report form that addressed demographics, HCV disease characteristics, liver fibrosis stage, and comorbidities, co-medications not intended for CHC, CHC treatment status, and laboratory data. The following data were added in the case report form for liver fibrosis stage : most recent stage of liver fibrosis, most recent biopsy results (if available), most recent FibroScan results (if available), most recent FibroTest results (if available), and respective dates of F0, F1, F2, F3, F4 stage evaluation. The METAVIR system was used to score the degree of hepatic fibrosis based on histopathologic evaluation, with F0 corresponding to no fibrosis, F1 corresponding to portal fibrosis without septa, F2 corresponding to portal fibrosis with few septa, F3 corresponding to septal fibrosis, and F4 corresponding to cirrhosis (9).

The study was performed in accordance with the Declaration of Helsinki and all applicable legislation, and all necessary ethical approval was received. The Central Ethics Committee for this study was Ethisch Comité - UZ Ghent.

2.2 Statistical Methods

Enrolment was planned for 300 patients, based on the recruiting capacity over the 3-month recruitment period of the 16 participating treatment centres across Belgium. The patients included in the study were representative of the Belgian HCV population. All statistical analyses were performed using the full analysis set (FAS), which included all patients satisfying all inclusion and exclusion criteria. Calculations were made using the available data in the FAS ; missing data were not replaced. All data obtained in this study were summarized using descriptive statistics. Subgroups of patient and disease characteristics were also described based on fibrosis stage category.

3. Results

3.1. Patient Demographics and Other Characteristics

A total of 303 patients were enrolled in the study and were included in the FAS (Table 1). The study included 151 men (49.8%) and 152 women (50.2%) ; the mean age of patients was 53.5 years (standard deviation [SD], 14.6 ; range, 19-89 years). The majority of patients were Caucasian (223 patients [73.6%]) ; 67 patients (22.1%) were African, 9 patients (3.0%) were Asian-, and 4 patients (1.3%) had another ethnic origin.

Of the 299 patients for whom data were available, 160 (53.5%) were born in Belgium, 65 (21.7%) were born in Sub-Saharan Africa, 12 (4.0%) were born in North Africa, and 62 (20.7%) were born in other countries. Belgium was the country of residence for 300 of the 303

Table 1. — **Demographic data**

Demographic data		*N*	*Mean (SD)*	*Min-Max*
Age (years)		303	53.5 (14.6)	19-89
BMI (kg/m²)		294	25.73 (5.23)	15.4-51.0
		N	*n*	*%*
Sex	*Men*	303	151	49.8
	Women	303	152	50.2
Ethnic origin	*Caucasian*	303	223	73.6
	African	303	67	22.1
	Asian	303	9	3.0
	Other	303	4	1.3
Country of residence	*Belgium*	303	300	99.0
	Democratic Republic of Congo	303	2	0.7
	Rwanda	303	1	0.3
Marital status	*Married or cohabitant*	296	158	53.4
	In a relationship	296	24	8.1
	Single (divorced)	296	45	15.2
	Single (not divorced)	296	69	23.3
Health insurance coverage		303	285	94.1
Homosexual practice		300		7.3
Referral route to liver clinic		*N*	*n*	*%*
General practitioner		303	121	39.9
Gastroenterologist		303	99	32.7
Other specialist		303	56	18.5
No referral		303	16	5.3
Other		303	11	3.6

BMI : body mass index ; Min : minimum ; Max : maximum ; SD : standard deviation.

Table 2. — **Current Onset of HCV Infection**

Current onset of HCV infection		*N*	*Mean (SD)*	*Min-Max*
Time since onset (years)		202	20.0 (14.0)	0–64
Age at onset (years)		202	32.6 (16.2)	0–87
Time since diagnosis (years)		283	12.3 (11.0)	0–53
		N	*n*	*%*
Number of infection	*First*	303	291	96.0
	Second	303	11	3.6
	Third	303	1	0.3
Country of onset	*Belgium*	255	179	70.2
	Sub-Saharan Africa (incl. Africa)	255	40	15.7
	Democratic Republic of Congo	255	16	6.3
	Other	255	36	14.1
Probable mode of infection	*Drug use (IV)*	204	77	37.7
	Drug use (non-IV)	204	8	3.9
	Blood transfusion	204	66	32.4
	Sexual	204	22	10.8
	Needle stick injury	204	11	5.4
	Dental procedure	204	7	3.4
	Other invasive procedure	204	8	3.9
Genotype	*1*	293	140	47.8
	1a	293	57	19.5
	1b	293	77	26.3
	2	293	12	4.1
	3	293	37	12.6
	4	293	79	27.0
	5	293	25	8.5
	6	293	0	0.0

HCV : hepatitis C virus ; incl. : including ; IV : intravenous ; Min : minimum ; Max : maximum ; SD : standard deviation.

patients (99.0%) and a high proportion of patients (285 [94.1%]) had health insurance.

Some notable differences were observed for age, sex, and health insurance coverage by fibrosis stage, but this was not observed for the other variables examined. Women made up 52.9% of the F0 population, 54.9% of the F0/F1 or F1 population, 40.8% of the F1/F2 or F2 population, 52.4% of the F3 population, and 33.3% of the F4 population.

Overall, 5.9% of patients did not have health insurance. This was the case for 1.4%, 4.4%, 6.6%, 4.8%, and 40.0% of patients in the F0, F0/F1 or F1, F1/F2 or F2, F3, and F4 groups, respectively.

Twenty-two patients (7.3%) reported homosexual practice. This was the case for 2.9% of the F0 population, 6.3% of the F0/F1 or F1 population, 14.5% of the F1/F2 or F2 population, 4.8% of the F3 population and 6.7% of the F4 population.

Most patients were referred to the clinic for the treatment of CHC infection by their general practitioner (121 patients [39.9%]) or by a gastroenterologist (99 patients [32.7%]), while 56 patients (18.5%) were referred by another specialist and 11 patients (3.6%) were referred via other means.

3.2 Current HCV Infection

The majority of patients had HCV genotype 1 infection (140/293 ; 47.8%) ; of these patients, 40.7% (57/140) had subtype 1a and 55.0% (77/140) had subtype 1b. There were also 79 patients (27.0%) with genotype 4, 37 patients (12.6%) with genotype 3, 25 patients (8.5%) with genotype 5, and 12 patients (4.1%) with genotype 2 ; no patients had genotype 6. For the vast majority of patients (291/303 ; 96%), the current HCV infection was their first HCV infection (Table 2).

The mean time since onset of the current HCV infection was 20.0 years, (SD, 14.0), and the mean age at onset of the current HCV infection was 32.6 years (SD, 16.2). The mean time since diagnosis was 12.3 years (SD, 11.0). The country of current HCV infection onset was Belgium for most patients (179/255 ; 70.2%). The probable mode of infection was identified in 204 of the 303 patients and included intravenous (IV) drug use for 77 patients (37.7%), blood transfusion for 66 patients (32.4%), sexual transmission for 22 patients (10.8%), needle stick injury for 11 patients (5.4%) patients, non-IV drug use for 8 patients (3.9%), dental procedure for 7 patients (3.4%), and another invasive procedure for 8 patients (3.9%).

Some notable differences between fibrosis stage categories were observed for time since current HCV infection onset and time since diagnosis of current HCV infection. The average time since current HCV infection onset was 22.2 years for F0 patients, 21.6 years for F0/F1 or F1 patients, 17.1 years for F1/F2 or F2 patients, 18.9 years for F3 patients, and 11.7 years for F4 patients. The

Table. 3. — **CHC treatment**

Treatment status	*N*	*n*	*%*	*95% CI*
CHC treatment-naive	303	217	71.6	66.2-76.6
CHC treatment-experienced	303	86	28.4	23.4-33.8
		N	*n*	*%*
Number of previous courses *1*		86	76	88.4
2		86	9	10.5
3		86	1	1.2
Most recent treatment		*N*	*n*	*%*
(Pegylated) interferon alpha ± ribavirin		85	73	85.9
Pegylated interferon alpha, ribavirin + protease inhibitor		85	7	8.2
Clinical trial drug		85	4	4.7
Ribavirin, sofosbuvir		85	1	1.2
Response to prior treatments		*N*	*n*	*%*
Null response[1]		84	26	31.0
Partial response[2]		84	5	6.0
Through[3]		84	4	4.8
Relapse[4]		84	34	40.5
SVR followed by reinfection[5]		84	7	8.3
Discontinuation[6]		84	8	9.5

[1] Failed to achieve a 1 $\log^{10}$ IU/mL reduction in HCV RNA by Week 4 or a 2 $\log^{10}$ IU/mL reduction in HCV RNA by Week 12 and failed to achieve HCV RNA undetectable thereafter.
[2] Achieved at least a 1 $\log^{10}$ IU/mL reduction in HCV RNA by Week 4 or a 2 $\log^{10}$ IU/mL reduction in HCV RNA by Week 12, but failed to achieve HCV RNA undetectable thereafter.
[3] Re-appearance of detectable HCV RNA at any time during treatment and after virologic response (HCV RNA undetectable).
[4] HCV RNA undetectable at the end of the treatment period but HCV RNA detectable following cessation of treatment.
[5] SVR: undetectable HCV RNA level (<50 IU/mL), 12 to 24 weeks after the end of treatment.
[6] Did not meet any definition of treatment failure (null response, partial response, breakthrough or relapse) and discontinued therapy prior to a full course of treatment.
CI : confidence interval ; CHC : chronic hepatitis C ; HCV : hepatitis C virus ; SVR : sustained virologic response.

Table 4. — **Liver fibrosis stage**

Liver fibrosis stage		*N*	*n*	*%*	*95% CI*
Most recent stage	*F0*	295	70	23.7	19.0-29.0
	F0/F1 or F1	295	113	38.3	32.7-44.1
	F1/F2 or F2	295	76	25.8	20.9-31.2
	F3	295	21	7.1	4.5-10.7
	F4 (Child-Pugh A)	295	15	5.1	2.9-8.2
METAVIR fibrosis score available		89			-
		N	*n*		*%*
Most recent fibroscan	*<8.8*	260	214		82.3
score (kPa)	*8.8–9.59*	260	15		5.8
	9.6–14.59	260	19		7.3
	≥14.6	260	12		4.6
Most recent fibrotest	*≤0.21 – F0*	84	24		28.6
score	*0.22–0.27 – F0/F1*	84	5		6.0
	0.28–0.31 – F1	84	3		3.6
	0.32–0.48 – F1/F2	84	22		26.2
	0.49–0.58 – F2	84	15		17.9
	0.59–0.72 – F3	84	8		9.5
	0.73–0.74 – F3/F4	84	2		2.4
	≥0.75 – F4	84	5		6.0
Oesophageal varices present		231	5		2.2
History of liver decompensation (currently compensated)		302	4		1.3

CI : confidence interval.

Table 5. — **Comorbidities**

Co-infections or comorbidities	*N*	*n*	*%*	
Any	303	211	69.6	
Co-infections				
	N	*n*	*%*	*95% CI*
HIV	303	23	7.6	4.9-11.2
Hepatitis B	303	3	1.0	0.2-2.9
Other	303	0	0.0	–

Comorbities		*N*	*n*	*%*
Liver and CHC-related	*Steatosis (non-alcoholic)*	303	11	3.6
	Cryoglobulinemia	303	8	2.6
	Alcoholic liver disease	303	4	1.3
	Hepatocellular carcinoma	303	2	0.7
	Autoimmune skin disease	303	1	0.3
	Primary biliary cirrhosis	303	1	0.3
Other (≥10 patients)	*Cardiovascular disease*	303	78	25.7
	Hypertension	303	67	22.1
	Coronary artery disease	303	11	3.6
	Diabetes mellitus	303	44	14.5
	Type 2	303	41	13.5
	Chronic pulmonary disease	303	20	6.6
	Lipid disorder	303	20	6.6
	Psychiatric disorders	303	60	19.8
	Depression	303	49	16.2
	Psychoactive substance dependency	303	14	4.6
	Opiate substitution	303	13	4.3
	Other	303	82	27.1
Alcohol consumption	*None*	300	131	43.7
	Occasional	300	123	41.0
	Regular	300	21	7.0
	Alcohol addiction	300	9	3.0
	Previous alcohol addiction	300	16	5.3
Smoking	*Never smoked*	300	140	46.7
	Ex-smoker	300	64	21.3
	Current smoker	300	96	32.0

CI : confidence interval ; CHC : chronic hepatitis C.

average time since diagnosis of current HCV infection was 13.2 years for F0 patients, 14.2 years for F0/F1 or F1 patients, 10.8 years for F1/F2 or F2 patients, 11.1 years for F3 patients, and 6.1 years for F4 patients.

3.3. CHC Treatment

Of the patients included in the study, 86 (28.4%) were CHC treatment-experienced and the majority of patients had been treated with one single course of prior therapy (Table 3). For the 85 treatment-experienced patients with available data, the most frequent prior treatments were IFN-alpha used with or without ribavirin (in 73 patients [85.9%]). Of the 84 treatment-experienced patients for whom response to treatment was documented, 34 (40.5%) experienced a relapse, 26 (31.0%) had no response, 5 (6.0%) had partial response to treatment, 8 (9.5%) discontinued the treatment, and 4 (4.8%) had virologic breakthrough. Sustained virologic response was followed by reinfection in 7 patients (8.3%).

3.4. Liver Fibrosis Stage

Fibrosis was determined in the majority of patients with a recent FibroScan (% of patients) and the second most commonly used test was biopsy (% of patients). In the 295 patients for whom the liver fibrosis stage was recorded, the liver fibrosis stage was F0 for 70 patients (23.7%), F0/F1 or F1 for 113 patients (38.3%), F1/F2 or F2 for 76 patients (25.8%), F3 for 21 patients (7.1%), and F4 (compensated cirrhosis [Child-Pugh A]) for 15 patients (5.1% ; Table 4).

Oesophageal varices were recorded in 5 patients (2.2%), and 4 patients (1.3%) had a history of liver decompensation, which was under control at the time of the study.

3.5. Comorbidities

In total, ≥1 comorbidity (co-infection, liver and CHC-related comorbidity, or other comorbidity), was recorded for 211 patients (69.6%). HIV co-infection was recorded for 23 patients (7.6%) and hepatitis B co-infection was recorded for 3 patients (1.0% ; Table 5).

No other co-infections were recorded.

Among liver and CHC-related comorbidities, cryoglobulinemia was recorded for 8 patients (2.6%), alcoholic liver disease was recorded for 4 patients (1.3%), hepatocellular carcinoma was recorded for 2

Table 6. — **Most frequent co-medications not Intended for CHC (≥10 patients)**

Number of co-medications not for CHC	*N*	*n*	*%*
0	303	75	24.8
1	303	53	17.5
2	303	47	15.5
≥3	303	128	42.2
Anatomical classes and most frequent therapeutic classes (≥10 patients)		*n*	*%*
A: Alimentary tract and metabolism		90	29.7
A02: Drugs for acid-related disorders		52	17.2
A10: Drugs used in diabetes		40	13.2
A11: Vitamins		18	5.9
B: Blood and blood-forming organs		44	14.5
C: Cardiovascular system		102	33.7
C03: Diuretics		24	7.9
C07: Beta-blocking agents		49	16.2
C08: Calcium channel blockers		29	9.6
C09: Agents acting on the renin-angiotensin system		52	17.2
C10: Lipid modifying agents		26	8.6
G: Genito-urinary system and sex hormones		11	3.6
H: Systemic hormonal preparations, excl. sex hormones and insulins		30	9.9
H03: Thyroid therapy		24	7.9
J: Anti-infectives for systemic use		25	8.3
M: Musculo-skeletal system		21	6.9
M01: Anti-inflammatory and antirheumatic products		11	3.6
N: Nervous system		117	38.6
N02: Analgesics		23	7.6
N05: Psycholeptics		68	22.4
N06: Psychoanaleptics		49	16.2
N07: Other nervous system drugs		38	12.5
R: Respiratory system		27	8.9
R03: Drugs for obstructive airway disease		18	5.9
R06: Antihistamines for systemic use		10	3.3

CHC : chronic hepatitis C.

patients (0.7%), and autoimmune skin disease and primary biliary cirrhosis were recorded for 1 patient each (0.3%).

The most frequently recorded comorbidities included cardiovascular disease, which was present in 78 patients (25.7% ; hypertension in 67 patients [22.1%] and coronary artery disease in 11 patients [3.6%]) ; psychiatric disorders, which was present in 60 patients (19.8% ; depression in 49 patients [16.2%]) ; diabetes mellitus in 44 patients (14.5% ; type 2 in 41 patients [13.5%]) ; chronic pulmonary disease in 20 patients (6.6%) ; lipid disorder in 20 patients (6.6%) ; and psychoactive substance dependency in 14 patients (4.6% ; opiate substitution in 13 patients [4.3%]).

Alcohol consumption was assessed as none for 131 patients (43.7%), occasional for 123 patients (41.0%), regular for 21 patients (7.0%), addiction for 9 patients (3.0%), and previous addiction for 16 patients (5.3%).

3.6. Co-Medications Not Intended for CHC

At the time of the study, 75 patients (24.8%) reported no co-medications, 53 patients (17.5%) reported 1 co-medication, 47 patients (15.5%) reported 2 co-medications, and 128 patients (42.2%) reported ≥3 co-medications.

The most frequently reported classes of co-medications that were not used to treat CHC infection (in ≥10 patients) are summarized in Table 6. The classes of co-medication included “nervous system” (117 patients [38.6%]), “cardiovascular system” (102 patients [33.7%]), “alimentary tract and metabolism” (90 patients [29.7%]), “blood and blood-forming organs” (44 patients [14.5%]), “systemic hormonal preparations, excluding sex hormones and insulins” (30 patients [9.9%]), “respiratory system” (27 patients [8.9%]), “anti-infective for systemic use” (25 patients [8.3%]), “musculo-skeletal system” (21 patients [6.9%]), and “genito-urinary system and sex hormones” (11 patients [3.6%]).

All 23 patients who had HIV co-infection were receiving antiretroviral treatment at the time of the study.

3.7 Reasons for Non-Eligibility for INF-Free Regimens

The most frequent individual reasons that patients were not eligible to initiate an IFN-free regimen included “regimen not reimbursed (access limitation)” in 257 patients (84.8%), “no urgency to treat – medical decision

Table 7. — **Reason for ineligibility to start interferon-free regimen**

Reason for ineligibility	*N*	*n*	*%*
Regimen not reimbursed (access limitation)	303	257	84.8
No urgency to treat – medical decision to wait	303	82	27.1
Waiting for future treatment option	303	25	8.3
No social insurance coverage	303	11	3.6
Other	303	9	3.0
Cost	303	7	2.3
Presumed impact on social life	303	7	2.3
Inconvenience (e.g., duration of treatment, number of pills)	303	6	2.0
Contraindication to IFN-free regimen	303	5	1.7
Presumed impact on ability to work	303	5	1.7
Presumed impact on family life	303	5	1.7
Presumed compliance/adherence issue	303	5	1.7
Patient unwilling to be treated	303	4	1.3
Presumed lack of efficacy	303	4	1.3
Presumed tolerability issue	303	2	0.7
Contraindication to ribavirin	303	1	0.3
No existing retreatment option	303	1	0.3

IFN : interferon.

Table 8. — **Laboratory data**

Most recent laboratory parameter result		*N*	*n*	*%*
HCV RNA viral load	*Low viral load*[1]	287	133	46.3
	High viral load[2]	287	109	38.0
	Positive qualitative test	287	45	15.7
CD4 T-cell count in HIV patients (cells/mm^3)	*<50*	23	1	5.9
	350-500	23	2	11.8
	>500	23	14	82.4
Detectable HIV-RNA		23	8	44.4
Receiving current ARV treatment		23	23	100

Laboratory parameter status	*Below NR*		*Within NR*		*Above NR*	
	n	*%*	*n*	*%*	*n*	*%*
Haemoglobin	30	10.5	253	88.8	2	0.7
Neutrophils	31	11.7	228	86.0	6	2.3
Platelets	17	5.9	270	94.1	0	0.0
Prothrombin time	5	6.5	19	24.7	53	68.8
INR	1	0.5	209	94.1	12	5.4
ALT		NA	109	36.7	188	63.3
AST		NA	137	46.9	155	53.1
GGT		NA	89	33.6	176	66.4
Albumin	8	3.8	198	95.2	2	1.0
Total bilirubin	4	1.4	263	94.6	11	4.0
Creatinine		NA	260	97.0	8	3.0
Alpha-fetoprotein		NA	175	91.6	16	8.4

[1]≤2 million copies/mL or ≤800,000 IU/mL ; [2]>2 million copies/mL or >800,000 IU/mL ; ALT : alanine aminotransferase ; ARV : antiretroviral ; AST : aspartate aminotransferase ; GGT : gamma-glutamyltransferase ; HCV : hepatitis C virus ; INR : International Normalized Ratio ; NA : not applicable ; NR : normal range.

to wait" in 82 patients (27.1%), "waiting for future treatment option" in 25 patients (8.3%), and "no social insurance coverage" in 11 patients (3.6% ; Table 7).

When analysing subgroups based on fibrosis stage category, in patients with low-grade fibrosis (F0, F0/F1, or F1), the main reasons for ineligibility were "no urgency to treat – medical decision to wait" and "regimen not reimbursed." Patients with fibrosis stage F1/F2 or F2 were also ineligible because of "regimen not reimbursed," whereas patients with high-grade fibrosis (F3 or F4) were generally ineligible because they were not covered by any social insurance. Reasons given other than ineligibility due to a lack of insurance for patients with fibrosis stage F4 included "regimen not reimbursed" for 4 patients (1.3%), "no urgency to treat/medical decision to wait" and "patient unwilling to be treated" for 2 patients (0.7%), and "waiting for future treatment option" for 1 patient (0.3%). Other reasons for patients with fibrosis stage F3 included "regimen not reimbursed" for 12 patients (4.0%), "no urgency to

treat/medical decision to wait" for 2 patients (0.7%), and "contraindication to IFN-free regimen," "presumed lack of efficacy," and "presumed compliance/adherence issue" for 1 patient each (0.3%).

3.8 Laboratory Data

Of the 287 patients with available data for the most recent HCV RNA test, 133 (46.3%) had a viral load of ≤2 million copies/mL or ≤800,000 IU/mL, 109 (38.0%) had a viral load >2 million copies/mL or >800,000 IU/mL, and 45 (15.7%) had a positive qualitative result (Table 8).

Notable results for laboratory parameters were found for haemoglobin (10.5% of patients below the normal range), neutrophils count (11.7% of patients below the normal range), prothrombin time (68.8% above the normal range), alanine aminotransferase (63.3% of patients above the normal range), aspartate aminotransferase (53.1% of patients above the normal range), and gamma-glutamyltransferase (66.4% of patients above the normal range). Eleven patients (4.0%) with available data had total bilirubin above the normal range.

For the 23 patients with HIV co-infection with available data, 1 (5.9%) had a most recent CD4 T-cell count of <50 cells/mm^3, 2 (11.8%) had a most recent CD4 T-cell count of 350 to cells/mm^3, and 14 (82.4%) had a most recent CD4 T-cell count of >500 cells/mm^3. HIV-RNA was detectable (HIV-RNA levels between <20 to 80,200 copies/mL) for 8 (44.4%) of the 18 patients with available data.

4 Discussion

To our knowledge, this is the first observational study analysing demographic, disease, and treatment characteristics in patients with CHC infection in Belgium who were not eligible for IFN-free treatment. This cross-sectional survey provides a valid and accurate assessment of this population of patients in 2016.

At the time this study was conducted, reimbursement of new-generation DAAs for the treatment of patients with CHC infection in Belgium was restricted to patients with advanced fibrosis (fibrosis stages F3 or F4). Since January 2019, reimbursement has been expanded to all patients suffering from chronic hepatitis C (F0-F4).

The patient population that were not eligible for IFN-free treatment reflected the reimbursement strategy in terms of fibrosis stage in place at the time the study was conducted. Only a limited percentage of patients had fibrosis stage F3 or F4 (approximately 12%), while the majority had low-grade fibrosis (approximately 60% with stage F0, F0/F1, or F1) and 25% had moderate fibrosis with stage F1/F2 or F2 (22% had a F2 score). In line with the reimbursement strategy, patients with low-grade fibrosis were mainly ineligible to receive IFN-free treatment because of a lack of urgency or a medical decision to wait and the lack of reimbursement of the regimen. The latter was also the most common reason for treatment ineligibility for patients with moderate fibrosis, whereas patients with high-grade fibrosis were generally ineligible because they were not covered by any social insurance.

The mean age was similar in patients with low-grade or moderate fibrosis (F0–F2 stages, mean age of approximately 50 years), whereas the study population with advanced fibrosis was generally older (F4 stage, mean age of 61 years). Notably, women made up 50% of all patients enrolled, which is more than would be expected. The proportion of women was higher in the subgroup with low-grade fibrosis : approximately 54% of patients with F0/F1 scores were women compared with 41% of patients with F1/F2 or F2 scores and 44% of patients with F3/F4 scores. The majority of patients with fibrosis scores F0 to F3 (≥93%) were covered by health insurance ; however, only 60% of patients with an F4 score were covered by health insurance. No notable differences between subgroups by fibrosis stage category were observed for other demographic characteristics analysed in this study.

Per observation of HCV genotype prevalence, regardless of fibrosis stage, the present study indicated that genotype 1 was most prevalent, with a majority of patients having genotype 1b : 77 patients (26.3%) *versus* 57 patients (19.5%) with genotype1a. These figures are in line with the prevalence figures mentioned in the yearly report of the Scientific Institute of Public Health of 2016 on HCV genotypes in serological tests performed in Belgium (10).

Genotype 1 was followed by genotype 4, genotype 3, genotype 5, and genotype 2. No patients had genotype 6. In a study conducted in Flanders and Brussels between 2001 and 2009 with 2301 patients with HCV infection, genotype 1 was the most prevalent genotype. However, in this study, genotype 3 was the second most prevalent genotype, followed by genotype 4, genotype 2, and genotype 5 ; only 1 patient had genotype 6 (11). Results from an observational study conducted between 2003 and 2004 in 9 Belgian hospital centres with 318 patients with HCV infection also identified genotype 1 as the most predominant genotype, followed by genotypes 3 and 4 (7). The slight difference in genotype distribution pattern observed in the present study could be due to the geographical range of study centres, which was designed to adequately reflect interregional variability in Belgium. Additional explanations could be the differences between patient groups (this study only included patients ineligible for IFN-free treatment), or the smaller numbers of patients studied (12).

The relatively high sexual transmission rate (10.8%) reported in this study could be partly explained by the proportion of African patients (67 patients [22.1%]) and patients with homosexual practice (22 patients [7.3%]). Among the latter, the probable mode of infection was reported as sexual for 16 patients (72.7%).

In this study, the mean age at onset of current HCV infection did not substantially differ between patients

with fibrosis stages F0 to F3 (range, 28-35 years), while patients with fibrosis stage F4 were slightly older at the time of diagnosis (mean, 45 years). The mean time since disease onset and diagnosis of current HCV infection gradually decreased with higher fibrosis score. These findings are in agreement with the results of an observational study in Brazil, which showed a significant correlation between age at diagnosis of HCV infection and fibrosis with degree of fibrosis increasing with advanced age (13).

The results of this study also showed that co-infection with HIV or hepatitis B occurred more frequently in patients with low-grade or moderate fibrosis. Patients with co-infection, account for about 8% of the study population. Other specific comorbidities (such as cryoglobulinemia, kidney transplantation, and dialysis) were observed in approximately 4% of patients with fibrosis stages F0 to F2 in the present study.

Since January 2019 reimbursement of IFN-free treatment regimens for patients with CHC infection in Belgium is currently available for all patients, even those with low-grade fibrosis (F0-F1) without specified comorbidities or co-infection, those regimens are fully accessible to patients with CHC infection without restrictions related to fibrosis stage in several other European countries, including France, Germany, the Netherlands, Ireland, Portugal, Iceland, and Poland (14). Retrospective cost of illness and modelling studies based on Belgian data demonstrated the cost-effectiveness of antiviral treatment initiation in patients with mild or moderate fibrosis, resulting in a significant reduction of healthcare costs and mortality in cases where sustained virologic response could be achieved (15-17). A recent report from the Belgian Health Care Knowledge Centre also indicated a greater gain in life-years and quality-adjusted life-years if treatment was initiated at an early stage (18). In view of these data, as well as the high efficacy of these DAA agents, expanding patient access to new DAA agents, which allow patients with CHC infection to obtain IFN-free treatment regardless of fibrosis stage and comorbidities. Such universal treatment with DAA agents greatly improve patient health and the associated HCV-related disease burden management in Belgium.

In conclusion, this observational study provides a unique description of the patient population with CHC infection requiring IFN-free treatment based on data collected in Belgium in 2016. The study included men and women in similar proportions (49.8% and 50.2%, respectively).

Mean age of patients was 53.5 years. The majority of patients were Caucasian (73.6%). The country of current HCV infection acquisition greatly differed among the study population, though Belgium was the country of current HCV infection acquisition for most patients (70.2%). Genotype 1 was the most prevalent genotype (47.8%) with a prevalence of 26.3% for genotype 1b.The probable modes of infection were mainly IV drug use (37.7%) and blood transfusion (32.4%). The most prevalent liver fibrosis stage were F0/F1 or F1 (38.3%), F1/F2 or F2 (25.8%) and F0 (23.7%). Overall, 69.6% of patients had at least 1 comorbidity, with HIV co-infection reported for 7.6% of patients and hepatitis B co-infection for 1.0% of patients. The most frequent individual reason for non-eligibility to IFN-free regimen was “regimen not reimbursed (access limitation)” for 85% of patients. These data could help medical communities and governmental agencies manage HCV disease burden, as well as help develop strategies in the light of the emergence of new treatment options.

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