ORIGINAL ARTICLE

Clinical characteristics and antiviral therapy in patients infected with hepatitis C virus in the interferon-free era

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KEY WORDS

epidemiology, hepatitis C virus, interferon-free therapy

ABSTRACT

INTRODUCTION The highly effective and safe interferon (IFN)-free options were a breakthrough in the treatment of patients infected with hepatitis C virus (HCV).

OBJECTIVES The current analysis was designed to evaluate changes in the patient profile and antiviral treatment characteristics over time.

PATIENTS AND METHODS The study population consisted of 963 consecutive HCV-infected patients who started IFN-free regimens between July 2015 and December 2020 in the Department of Infectious Diseases in Kielce, Poland. The analysis was carried out for 5 time intervals.

RESULTS The studied group was sex-balanced, with the median (interquartile range) age changing from 58 (44.8–63) in 2015–2016 to 43 (35–61) in 2020. The proportion of patients with comorbidities decreased over the years. The rate of treatment-naïve individuals increased from 40.9% in 2015–2016 to 91% in 2020, while the percentage of patients with liver cirrhosis decreased from 51.1% in 2015–2016 to 13.3% in 2020. Genotype-specific regimens dominated in the years 2015–2017, while pangenotypic options gained an advantage in 2019 and reached 91% in 2020. Overall effectiveness achieved 98.4% in the per-protocol analysis and was comparable over the years with lower efficacy among patients with liver cirrhosis and those infected with genotype 3. The therapy was well-tolerated, and the safety profile improved over time.

CONCLUSIONS The median age of HCV-infected patients decreased over the years. They were less burdened with comorbidities and comedications, more likely to be treatment-naïve, and had less advanced liver disease. The genotype-specific regimens, predominantly used at the beginning of the IFN-free era, were superseded by the pangenotypic regimens.

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Received: April 4, 2022.
Revision accepted: June 20, 2022.
Published online: June 28, 2022.
Pol Arch Intern Med. 2022;
132 (9): 16282
doi:10.20452/pamw.16282

INTRODUCTION According to the most recent data provided by the World Health Organization (WHO), there are 58 million people globally chronically infected with hepatitis C virus (HCV).[1] Nearly 400 000 deaths each year caused by chronic hepatitis C (CHC) are reported worldwide, mainly from its severe complications, including liver cirrhosis and hepatocellular carcinoma (HCC).[2]

The risk of progression of liver fibrosis leading to cirrhosis equals 20%, but the incidence varies with the host and viral predictors, one of which is the HCV genotype (GT).[2] In the era of interferon (IFN)-based regimens, HCV genotype was also one of the most important predictors determining the effectiveness of antiviral therapy. At that time, GT1 and GT4-infected patients treated with pegylated IFN (pegIFN) and ribavirin (RBV) were considered "difficult to treat" due to lower effectiveness when compared with GT2- and GT3-infected individuals.[3,4] The situation changed with the availability of the first direct-acting antivirals (DAA) in 2011, telaprevir and boceprevir, which were registered to use with pegIFN+RBV in patients with GT1 infection only, while the combination with the next-generation DAAs, simeprevir (SMV), and daclatasvir (DCV) widened the therapeutic options

WHAT'S NEW?

The introduction of interferon-free therapy was a revolution in the treatment of patients infected with hepatitis C virus (HCV), and raised the hope of eliminating HCV as a significant public problem. This analysis describes changes in patient characteristics and therapeutic options along with their efficacy and safety over the years. We believe that our research, which also covers the time of the COVID-19 pandemic, provides valuable data to predict HCV eradication. Furthermore, it can contribute to ensuring the highest standard of care tailored to the treated population.

also for GT4-infected patients.[5-7] The possibility of using triple therapy in patients infected with all HCV genotypes appeared with the registration of sofosbuvir (SOF), the first drug to be used without IFN, thus opening the era of IFN-free therapy in the treatment of HCV.[8]

DAAs became available to Polish patients in mid-2015 under a therapeutic program reimbursed by the Polish National Health Fund (Narodowy Fundusz Zdrowia, NFZ). From the beginning, there were no limitations regarding liver fibrosis, genotype, history of previous therapy, and co-infections. The order of treatment and the choice of the therapeutic regimen were entirely decided by the attending physician, guided by the stage of the liver disease, previous ineffective therapies, and according to the current medical knowledge, recommendations of the Polish Group of Expert for HCV (PGE HCV), and drug labels.[9-13] Initially, due to the long waiting list of patients, priority was given to those who previously had limited access to the therapy due to IFN contraindications or intolerability, and to patients who were expected to have poor treatment outcomes.

The patients with liver cirrhosis were a special group awaiting therapy, whom the substantially higher efficacy and a better safety profile of DAA offered a chance for the effective treatment.

The prognosis of patients infected with GT3, for whom the only available IFN-free option at the beginning of the DAA era was a suboptimal regimen of SOF+RBV, improved with the introduction of pangenotypic regimens.[14,15] The prioritization of particular patient groups, the emergence of new therapeutic options, and demographic changes in the HCV-infected population influenced the profile of patients treated during the several years of DAA availability.[15]

Analysis of the evolution of data is essential to provide the highest standard of care tailored to the population. Therefore, the current study was designed to evaluate the changes in patient profiles and HCV therapeutic options and to assess the treatment efficacy and safety in real world experience after more than 5 years of access to IFN-free therapy.

PATIENTS AND METHODS

Study population The data analyzed in the study were collected from consecutive patients with CHC who initiated antiviral treatment at the Department of Infectious Diseases, Provincial Hospital in Kielce, from July 1, 2015, through December 31, 2020. The treatment was based on IFN-free regimens fully reimbursed by the NFZ. The regimen, dosage, and length of the treatment course were selected by the treating physician from available therapeutic options and administered according to the protocol of the NFZ therapeutic program, product characteristics, and recommendations of the PGE HCV.[9-13]

Data collection The patients provided informed consent for the treatment and processing of their personal data. The data were collected retrospectively using a hospital database. The study population was divided into 5 groups based on the time of treatment initiation: 2015–2016, 2017, 2018, 2019, and 2020. These 5 groups were compared for demographic and clinical characteristics, including age, sex, body mass index (BMI), HCV genotype, comorbidities, concomitant medications, severity of liver disease, and treatment regimens.

Assessment of liver disease severity The stage of liver fibrosis was evaluated using real-time shear-wave elastography with an Aixplorer device (SuperSonic Imagine, Aix-en-Provence, France) and defined as F0–F4 according to the METAVIR score.[16] The cutoffs for the prediction of F0–F1 and F2 were adopted at the level of 5 and 7 kilopascals, respectively. Advanced liver fibrosis was determined as F3 and liver cirrhosis was determined as F4, and the cutoff levels of 9 and 13 kilopascals were used to predict F3 and F4, respectively.[17,18] The patients with liver stiffness corresponding to F4 were evaluated for the presence of esophageal varices and rated using the Child–Pugh scale.[19] Data regarding liver decompensation were captured before treatment and at the baseline. The incidence of HCC and liver transplantation was assessed before treatment.

Assessment of treatment effectiveness Sustained virological response (SVR) was the efficacy end point. It was defined as undetectable HCV RNA at least 12 weeks after the end of treatment (EOT). The concentration of HCV RNA was measured using the Xpert HCV Viral Load real-time assay (Cepheid, Sunnyvale, California, United States) with a lower limit of detection of 10 IU/ml. The patients lost to the follow-up were considered nonvirologic failures due to no HCV RNA assessment, whereas those with detectable viremia 12 weeks after the EOT were considered virologic nonresponders.

Assessment of safety Safety outcomes were collected during the treatment and followed for 12 weeks after the EOT. The following information was gathered during the treatment course and follow-up period: therapy course modification

TABLE 1 Baseline characteristics of patients in 5 time intervals

Parameter		2015–2016	2017	2018	2019	2020
Patients, n		176	202	271	201	113
Sex, n (%)	Women	102 (58)	101 (50)	158 (58.3)	113 (56.2)	51 (45.1)
	Men	74 (42)	101 (50)	113 (41.7)	88 (43.8)	62 (54.9)
Age, median (IQR)		58 (44.8–63)	53.5 (37–64.8)	46 (35–64)	42 (34–60)	43 (35–61)
	Women	59 (55.3–65)	59 (42–67)	49.5 (34.3–67)	41 (32–60)	43 (35.5–61.5)
	Men	52.5 (40–60)	48 (35–61)	43 (35–61)	42 (35.8–60)	43 (35–60.3)
BMI, kg/m^2, mean (SD); min-max		26.3 (4.5); 17.5–44.9	26.4 (4.4); 17.8–44.1	25.5 (4.5); 15.6–45	25.6 (4.7); 17.5–41.3	25.8 (4.3); 18.1–41.2
Comorbidities, n (%)						
Any comorbidity		152 (86.4)	154 (76.2)	219 (80.8)	149 (74.1)	78 (69)
Hypertension		76 (43.2)	75 (37.1)	96 (35.4)	53 (26.4)	37 (32.7)
Diabetes		35 (19.9)	26 (12.9)	30 (11.1)	16 (8)	10 (8.8)
Renal disease		17 (9.7)	20 (9.9)	26 (9.6)	6 (3)	13 (11.5)
Autoimmune diseases		22 (12.5)	2 (1)	23 (8.5)	18 (9)	3 (2.7)
Non-HCC tumors		6 (3.4)	5 (2.5)	18 (6.6)	15 (7.5)	8 (7.1)
Other		140 (79.5)	142 (70.3)	189 (69.7)	132 (65.7)	70 (61.9)
Concomitant medications, n (%)		134 (76.1)	130 (64.4)	172 (63.5)	126 (62.7)	59 (52.2)

Abbreviations: BMI, body mass index; HCC, hepatocellular carcinoma; IQR, interquartile range

or discontinuation, the occurrence of adverse events (AE), severe AEs, and death. AEs of particular interest, related directly to the liver function, involved gastrointestinal bleeding, ascites, and encephalopathy, and were monitored in patients with liver cirrhosis.

Ethics Ethics committee approval was not necessary. This observational study was conducted in real-world settings with registered medications. The patients were not exposed to any experimental interventions. The study did not change the patients' clinical management. The data were originally collected not for scientific purposes but to assess treatment efficacy and safety. Due to the study's retrospective design, patient consent was not required. Patient data were gathered and analyzed according to the applicable personal data protection principles.

Statistical analysis Continuous data were presented as mean (SD), median and interquartile ranges (IQR), whereas categorical data were expressed as numbers and percentages. All patients who initiated the treatment were included in the intent-to-treat (ITT) analysis. Per-protocol (PP) analysis appraised patients who had HCV RNA evaluation 12 weeks after the treatment completion.

RESULTS

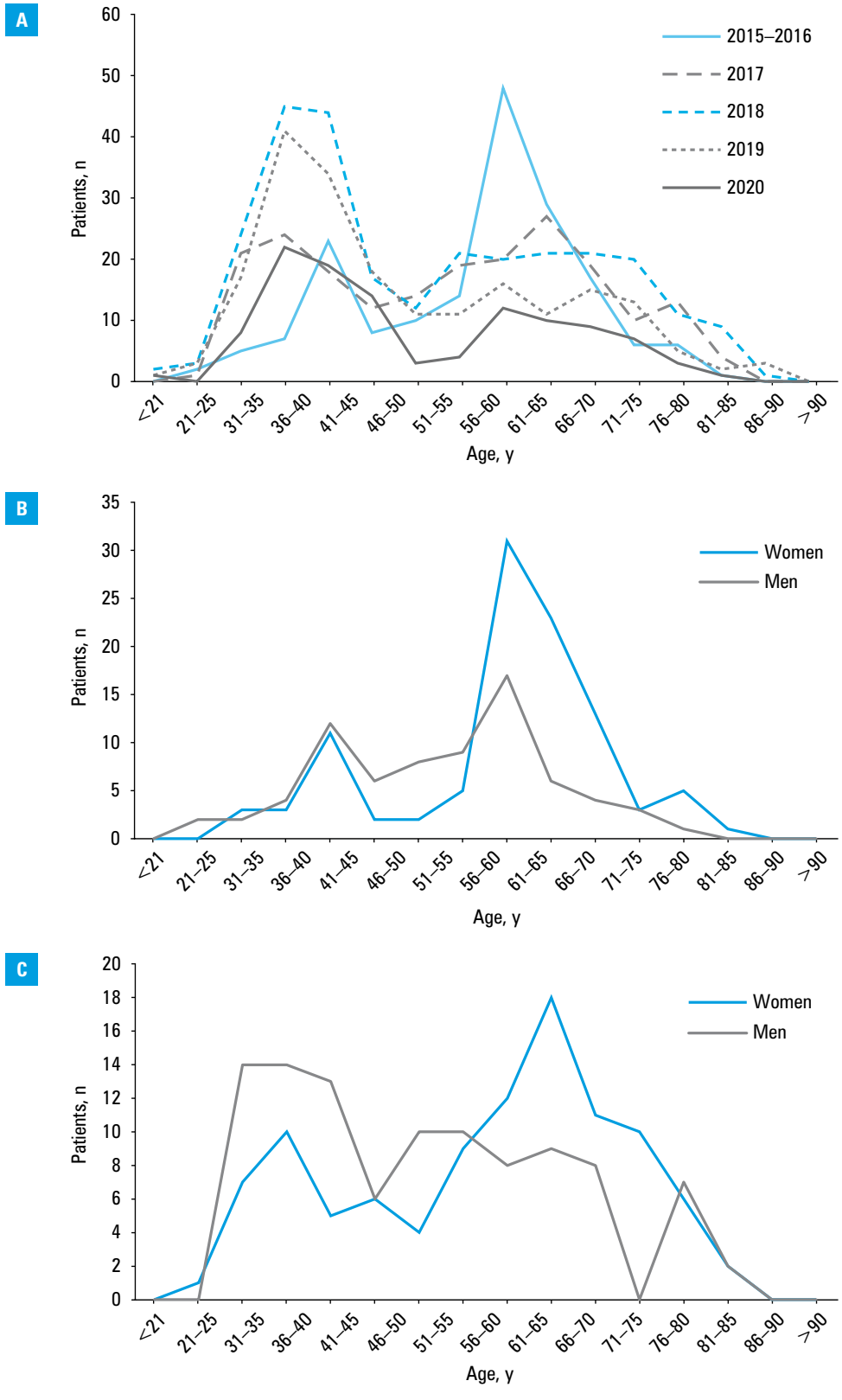
Patient characteristics A total of 963 patients were included in the analysis. The 5 groups, according to the date of therapy initiation, included 176 (2015–2016), 202 (2017), 271 (2018), 201 (2019), and 113 (2020) patients. The study population was sex-balanced, with a minor predominance of women until 2019, and slightly more men in 2020. A reduction in age was observed in consecutive years, both in men and women. The median (IQR) age at enrollment ranged from 58 (44.8–63) years in 2015–2016 to 43 (35–61) years in 2020. The majority of patients qualified for the treatment were over 30 years of age. Women were older, with a median (IQR) age of 59 (55.3–65) years in 2015–2016, and 43 (35.5–61.5) years in 2020. Men were older only in 2019, with a median (IQR) age of 42 (35.8–60) years (TABLE 1).

The age distribution graph demonstrates the increase in the number of patients treated at the age of 31 to 35 years as compared with the first time interval, where the age of treatment initiation showed 2 peaks, a lower one for 36–40 years, and a dominant one for 56–60 years (FIGURE 1).

The patient BMI remained nearly the same throughout all 5 time intervals (TABLE 1). The majority of patients included in the analysis had comorbidities, with the most common being arterial hypertension and diabetes at all time intervals. The prevalence of hypertension and diabetes decreased from 2015–2016 to 2019, and then it was higher in the last time interval. An upward tendency in 2020 was also visible in the case of patients with chronic kidney diseases. An increase in non-HCC tumors was recorded from 3.4% in 2015–2016 to 7.1% in 2020.

Along with the decrease in the proportion of comorbidities over the years, a systematic decline in the proportion of patients taking concomitant medications was documented, from 76.1% in 2015–2016 to 52.2% in 2020 (TABLE 1).

Characteristics of liver disease The most common genotype was GT1b for all 5 time intervals, with a reduction in percentage in favor of GT3 in


A
Patients, n
Age, y
2015–2016
2017
2018
2019
2020
B
Women
Men
C
<21
21–25
31–35
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66–70
71–75
76–80
81–85
86–90
>90

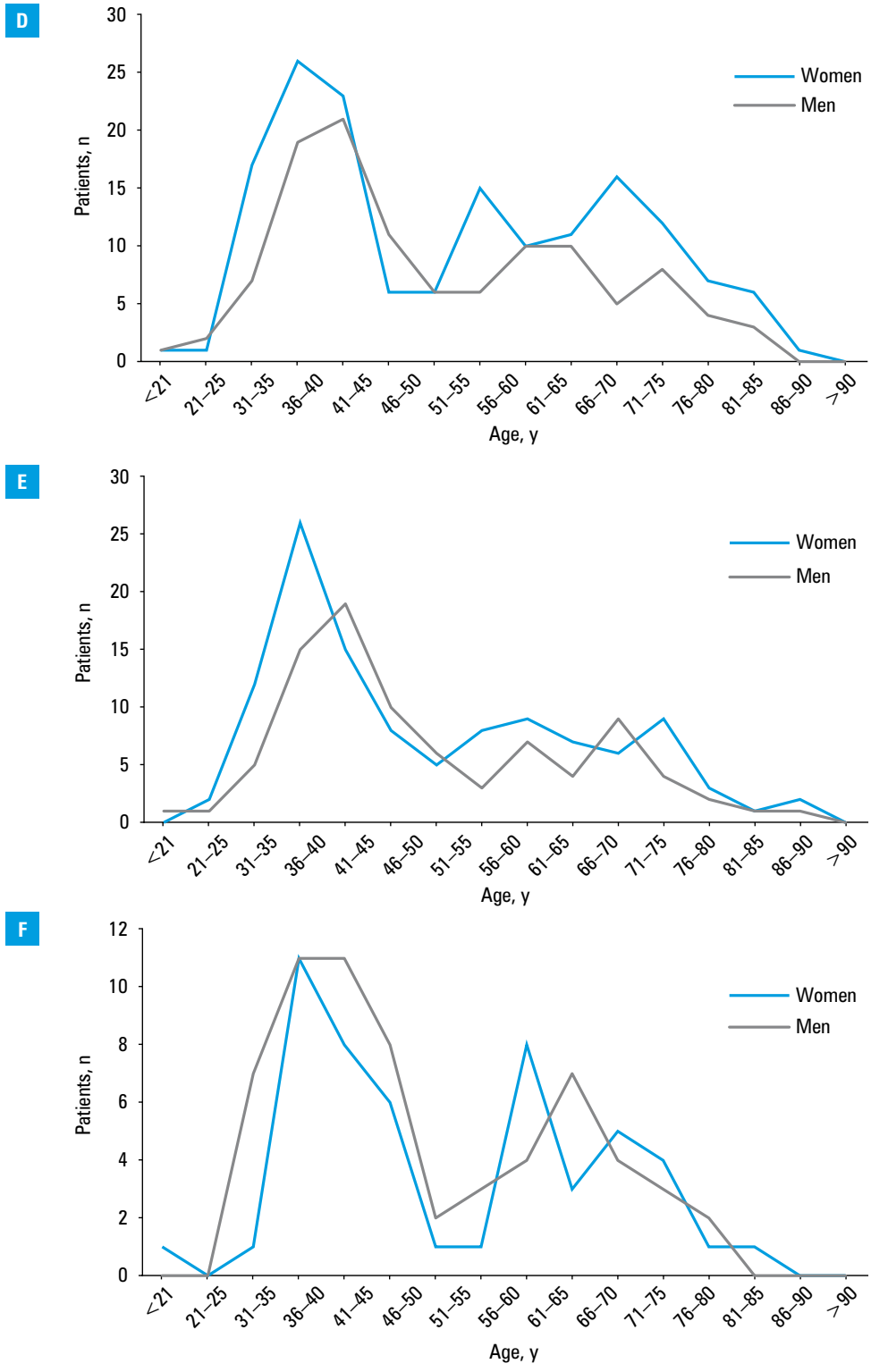

FIGURE 1 Age distribution in all patients treated in 5 time intervals (A) and in women and men in the following years: 2015–2016 (B), 2017 (C), 2018 (D), 2019 (E), 2020 (F)

2019 and 2020 (TABLE 2). A history of HCC and liver transplantation was documented more frequently at the beginning of the IFN-free era.

The rate of patients diagnosed with liver cirrhosis (F4) at the baseline decreased significantly from 51.1% in 2015–2016, through 22.3% in 2017, to 11.8% in 2018. An upward trend was observed in subsequent years, reaching 12.4% and 13.3% in 2019 and 2020, respectively. Additionally, the percentage of patients who scored B and C on the Child–Pugh scale increased in the last time interval to 33.4% (Supplementary material, *Table S1*).

Treatment characteristics The rate of treatment-naïve patients was 40.9% in 2015–2016 and then systematically increased at consecutive time intervals until 2019, when it was 94%, while in 2020, there was a slight decrease to 91.2% (TABLE 3).

The most common type of nonresponse in previous treatment failures was a null response in the first analyzed period and relapse during

TABLE 2 Characteristics of liver disease in 5 time intervals

Parameter	2015–2016	2017	2018	2019	2020
Patients, n	176	202	271	201	113
GT, n (%)					
1	0	0	9 (3.3)	15 (7.5)	10 (8.8)
1a	2 (1.1)	0	5 (1.8)	2 (1)	3 (2.7)
1b	156 (88.6)	179 (88.6)	221 (81.5)	157 (78.1)	84 (74.3)
2	0	0	0	0	0
3	11 (6.3)	18 (8.9)	23 (8.4)	24 (11.9)	13 (11.5)
4	7 (4)	5 (2.5)	11 (4)	3 (1.5)	3 (2.7)
5	0	0	0	0	0
6	0	0	2 (1)	0	0
Fibrosis, METAVIR score, n (%)					
F0	2 (1.1)	12 (5.9)	11 (4.1)	6 (3)	12 (10.6)
F1	34 (19.3)	80 (39.6)	169 (62.4)	132 (65.7)	57 (50.4)
F2	29 (16.5	30 (14.9)	34 (12.5)	25 (12.4)	21 (18.6)
F3	21 (12)	35 (17.3)	25 (9.2)	13 (6.5)	8 (7.1)
F4	90 (51.1)	45 (22.3)	32 (11.8)	25 (12.4)	15 (13.3)
History of HCC, n (%)	5 (2.8)	2 (1)	2 (0.7)	0	1 (0.9)
History of liver transplantation, n (%)	3 (1.7)	0	1 (0.4)	0	0
Extrahepatic manifestations, n (%)					
Any manifestation	95 (54)	117 (57.9)	150 (55.4)	110 (54.7)	55 (48.7)
Cryoglobulinemia	75 (42.6)	104 (51.5)	128 (47.2)	91 (45.3)	48 (42.5)
Thyroid abnormalities with antithyroid antibodies	20 (11.4)	22 (10.9)	17 (6.3)	23 (11.4)	4 (3.5)
Thrombocytopenia in patients without advanced liver fibrosis/cirrhosis and splenomegaly	4 (2.3)	6 (3)	14 (5.2)	6 (3)	7 (6.2)
Other	9 (5.1)[a]	0	8 (3)[b]	0	0
HIV coinfection, n (%)	0	0	2 (0.7)	0	0
HBV coinfection, n (%)					
Anti-HBc total (+) only	34 (19.3)	37 (18.3)	32 (11.7)	24 (11.9)	12 (10.6)
HBsAg(+); incl. HBV DNA(+)	2 (1.1); 1 (0.6)	3 (1.5); 0	1 (0.4); 1	1 (0.5); 1	0

a 3 cases of arthralgia without pathological changes in the joints, 2 cases of monoclonal gammopathy, Sjogren's syndrome, dryness syndrome, lichen planus, B-cell lymphoma

b 2 cases of monoclonal gammopathy, arthralgia without pathological changes in the joints, non-Hodgkin lymphoma, diffuse large B-cell lymphoma, alopecia areata, peripheral T cell lymphoma, porphyria cutanea tarda

Abbreviations: Anti-HBc, antibodies against hepatitis B core antigen; GT, genotype; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HIV, human immunodeficiency virus; others, see **TABLE 1**

the remaining time intervals. The most commonly used regimen in the previous treatment course was a combination of pegIFN and RBV until 2019 (58%–80%), whereas in 2020, half of the 10 previous ineffective therapies were IFN-free regimens.

The patients were treated with genotype-specific or pangenotypic options. Genotype-specific regimens included asunaprevir (ASV)+DCV, ombitasvir/paritaprevir±dasabuvir±RBV, ledipasvir/SOF±RBV, SOF+SMV±RBV, and grazoprevir/elbasvir±RBV combination. Pangenotypic regimens were divided into "old," available from the beginning of the IFN-free era and represented by SOF+RBV and SOF+DCV±RBV, and "new," registered later and made available for Polish patients since 2018, including glecaprevir/pibrentasvir and SOF/velpatasvir ± RBV. Among the currently used therapeutic options, genotype-specific regimens accounted for over 90% of treatments in 2015–2017, and in 2020 new pangenotypic regimens accounted for such a percentage (Supplementary material, *Figure S1*).

Treatment effectiveness A total 937 out of 963 patients responded to the therapy representing an SVR of 97.3% in the ITT analysis. After excluding 11 patients (1.1%) lost to the follow-up, the efficacy rate was 98.4%. The lowest effectiveness was achieved with SOF+RBV and ASV+DCV combinations, 93.9% and 94.1% in PP analysis, respectively. The remaining genotype-specific and pangenotypic regimens resulted in high and comparable effectiveness exceeding 98% (**TABLE 4**).

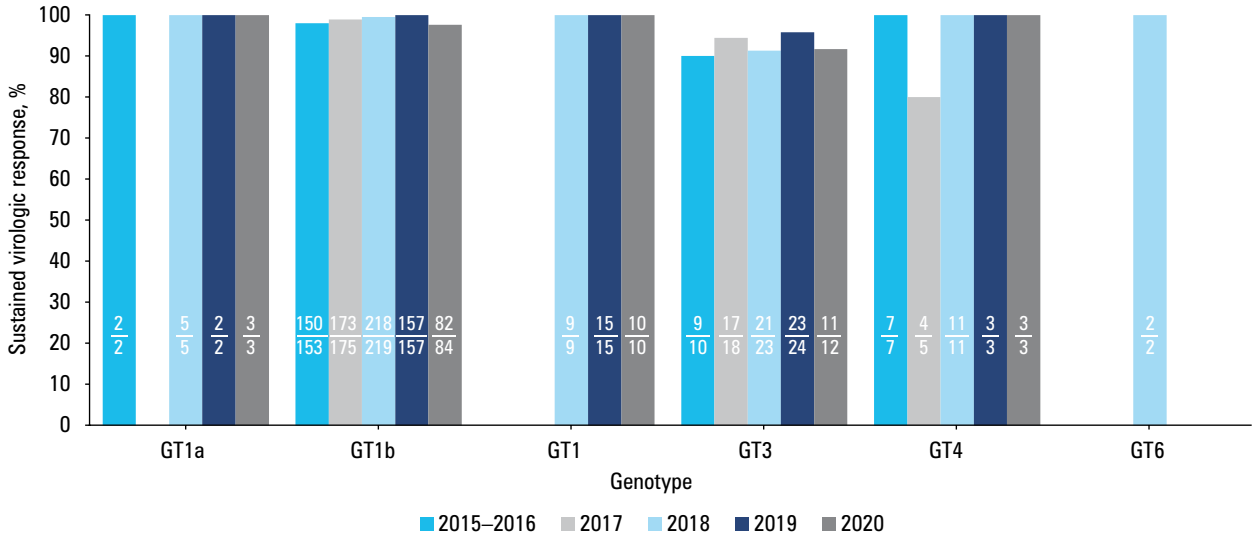

FIGURE 2 Sustained virologic response rates according to genotypes in 5 time intervals (per protocol analysis)
Abbreviations: see **TABLE 1**

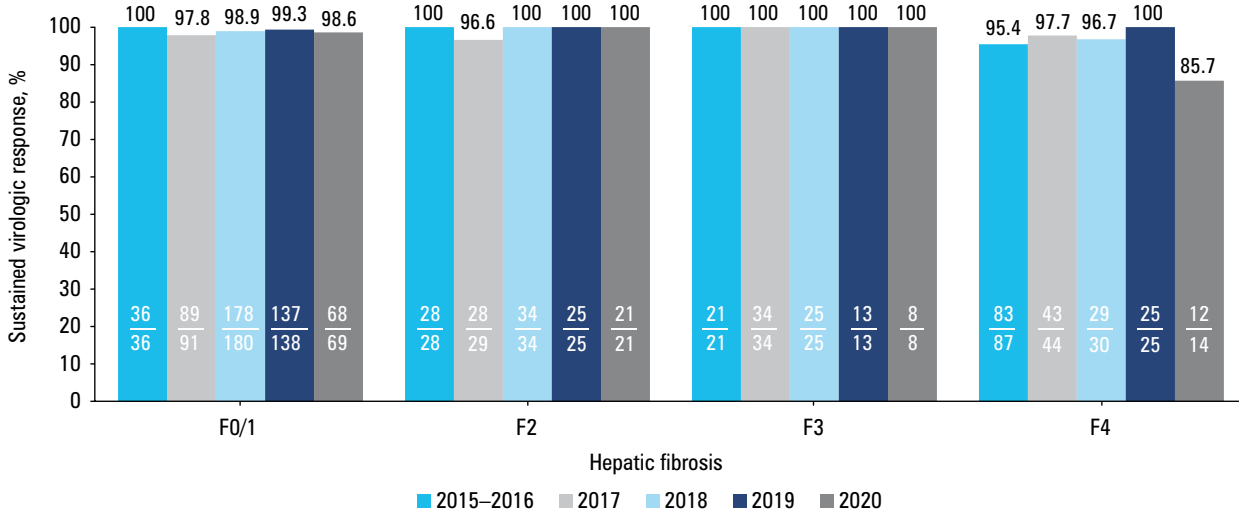

FIGURE 3 Sustained virologic response rates according to the grade of hepatic fibrosis in 5 time intervals (per protocol analysis)
Abbreviations: F, fibrosis

The response rates calculated for HCV genotypes were comparable over time. The lowest efficacy was documented in the patients infected with GT3 (**FIGURE 2**) and patients diagnosed with F4 liver fibrosis (**FIGURE 3**).

All 15 virologic nonresponders were men, of those 7 were treatment-experienced, including 3 DAA failures, 8 were infected with GT1b, and 8 had F4 liver fibrosis, and among them 3 scored B on the Child–Pugh scale (Supplementary material, *Table S2*).

Treatment safety The therapy was well-tolerated, as can be seen in Supplementary material, *Table S3*. The percentage of individuals who completed the treatment course according to the schedule increased over time (from 92.6% in 2015–2016 to 99.1% in 2020). Consequently, the percentage of patients with therapy modification or discontinuation decreased over the years. At successive time intervals, the prevalence of adverse events decreased from 28.4% in 2015–2016 to 13.3% in 2020. A similar tendency can be observed regarding serious AEs, AEs leading to treatment discontinuation, and deaths. The most common AEs, such as weakness / fatigue and anemia remained similar across the analyzed time intervals.

Increasing the safety profile over time was accompanied by a reduction of RBV-containing regimens (**TABLE 3**).

DISCUSSION The therapeutic program for patients with CHC covering IFN-free regimens was introduced in Poland in mid-2015. Our analysis was carried out taking into account all consecutive therapies conducted in a single hepatology center, which makes it unique from the beginning of the availability of DAA regimens. To date, only 3 large analyses of changes in the patient profile and HCV antiviral therapy have been published, and the most prolonged observation included the DAA era through 2019.[15,20,21] The current study documents changes in

TABLE 3 Treatment characteristics in 5 time intervals

Parameter	2015–2016	2017	2018	2019	2020
Patients, n	176	202	271	201	113
History of previous therapy, n (%)					
Treatment-naïve	72 (40.9)	152 (75.2)	243 (89.7)	189 (94)	103 (91.2)
Relapsers	32 (18.2)	21 (10.4)	12 (4.4)	8 (4)	5 (4)
Null responders	55 (31.3)	12 (6)	7 (2.6)	2 (1)	3 (3)
Discontinuation for safety reasons	17 (9.6)	17 (8.4)	9 (3.3)	2 (1)	2 (1.8)
Previous regimen in patients with treatment failure, n	104	50	28	12	10
IFN+RBV	13 (12.5)	4 (8)	0	0	1 (10)
PegIFN + RBV	60 (57.7)	40 (80)	19 (67.9)	9 (75)	4 (40)
PI+ PegIFN + RBV	29 (27.8)	6 (12)	4 (14.3)	0	0
SOF + PegIFN + RBV	1 (1)	0	1 (3.5)	0	0
IFN-free	1 (1)	0	4 (14.3)	3 (25)	5 (50)
Current treatment regimen					
ASV+DCV	9 (5.1)	10 (5)	0	0	0
OBV/PTV/r±DSV±RBV	100 (56.8)	73 (36.1)	60 (22.1)	0	0
LDV/SOF±RBV	52 (29.5)	59 (29.2)	61 (22.5)	6 (2.9)	0
SOF+RBV	10 (5.7)	18 (8.9)	6 (2.2)	0	0
SOF+SMV±RBV	4 (2.3)	0	0	0	0
SOF+DCV±RBV	1 (0.6)	1 (0.5)	0	0	0
GZR/EBR±RBV	0	41 (20.3)	56 (20.6)	49 (24.4)	10 (8.8)
SOF/VEL±RBV	0	0	35 (12.8)	54 (26.9)	35 (31)
GLE/PIB	0	0	53 (19.8)	92 (45.8)	68 (60.2)
RBV-containing therapies	84 (47.7)	16 (7.9)	16 (5.9)	5 (2.5)	12 (10.6)

Abbreviations: ASV, asunaprevir; DCV, daclatasvir; DSV, dasabuvir; EBR, elbasvir; GLE, glecaprevir; GZR, grazoprevir; IFN, interferon; LDV, ledipasvir; OBV, ombitasvir; PegIFN, pegylated interferon; PI, protease inhibitors; PIB, pibrentasvir; PTV, paritaprevir; r, ritonavir; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; VEL, velpatasvir

TABLE 4 Treatment effectiveness according to regimen, calculated as intent-to-treat and per protocol analysis

Regimen	SVR ITT, n/N (%)	SVR PP, n/N (%)
All regimens	937/963 (97.3)	937/952 (98.4)
OBV/PTV/r ± DSV ± RBV	229/233 (98.3)	229/232 (98.7)
OBV/PTV/r + DSV	193/194 (99.5)	193/194 (99.5)
OBV/PTV/r + RBV	11/12 (91.7)	11/12 (91.7)
OBV/PTV/r + DSV + RBV	25/27 (92.6)	25/26 (92.6)
LDV/SOF ± RBV	173/178 (97.2)	173/175 (98.9)
LDV/SOF	120/121 (99.2)	120/120 (100)
LDV/SOF + RBV	53/57 (93)	53/55 (96.4)
GZR/EBR ± RBV	152/156 (97.4)	152/153 (99.3)
VEL/SOF ± RBV	121/124 (97.6)	121/123 (98.4)
VEL/SOF	106/107 (99.1)	106/106 (100)
VEL/SOF + RBV	15/17 (88.2)	15/17 (88.2)
GLE/PIB	209/213 (98.1)	209/213 (98.1)
ASV+DCV	16/19 (84.2)	16/17 (94.1)
SOF + DCV ± RBV	2/2 (100)	2/2 (100)
SOF + RBV	31/34 (91.2)	31/33 (93.9)
SOF + SMV ± RBV	4/4 (100)	4/4 (100)

Abbreviations: ITT, intent-to-treat; n, number of SVR patients; N, total numer of patients in the analyzed regimen; PP, per protocol; SVR, sustained virologic response; others, see TABLE 3

the demographic and clinical data of CHC patients over more than 5 years. These data are a valuable source of information on predicting HCV eradication. The fact that our analysis also includes the COVID-19 pandemic period makes it unique. The WHO established the goal of eliminating HCV as a significant public threat by 2030. According to the analysis of Polish perspectives carried out in 2019, achieving this goal without the population screening was unrealistic.[1,22] In recent years, COVID-19 affected the number of diagnosed and treated patients, delaying the potential HCV elimination, not only in Poland.[22-24] The current analysis also confirms the reduction in the number of patients undergoing DAA therapy. While in 2019 the decrease in the number of patients treated for CHC resulted from the lack of a national screening program and the failure to detect HCV infection in patients unaware of the disease, in 2020 it was combined with the impact of the pandemic. Our findings are consistent with many national and global observations.[25-27]

Despite the lack of barriers in access to reimbursed DAA options at the level of a therapeutic program, at the beginning of the IFN-free era, physicians prioritized the treatment of patients with advanced liver fibrosis and cirrhosis. It was

also reflected in the current analysis and supported by other real-world studies.[15,20] In the first analyzed time interval, cirrhotic patients constituted more than half of all treated individuals. After that, the proportion of these patients decreased, and from 2019 it increased again. The documented growth in the percentage of patients with liver cirrhosis was not high but the trend continued into 2020. A possible explanation is the detection of HCV infection in patients at an advanced stage of the disease. In the absence of a national screening program, the scale of this phenomenon was not large but the tendency was clearly outlined. Further observations are necessary to determine whether this trend will continue. It is a worrying phenomenon given that DAA therapy in patients with liver cirrhosis is effective and safe, and HCV eradication reduces the risk of serious complications, including decompensation and HCC.[28,29]

Patients who previously failed antiviral therapy also had priority access to treatment at the beginning of the IFN-free era. In our analysis, they accounted for almost 60% of all treated individuals in 2015–2016, while in 2020, only 10 such patients, accounting for nearly 9%, were included in the study, and half of them were already DAA failures.

The age distribution of the treated population also evolved in successive time intervals. Patients treated with IFN-free therapy became younger over the years, so the proportion of those with comorbidities and receiving comedications decreased throughout the entire analyzed period.

A similar tendency was also reported by both Real World Evidence (RWE) studies concerning changes in the profile of CHC patients treated with DAA.[15,20,21] The irregularity in the age distribution was noted in all 5 time intervals. In 2015–2016, there were 2 visible peaks in the age of the population. Regardless of sex, the first included patients between 36 and 40 years of age, and the second those between 56 and 65 years. It seems to be distinctive for the Polish population.[15,30] However, in 2017 the dominant age group among men was 26–40 years. Interestingly, in 2018, the same age distribution became dominant also among women. The tendency was observed both in men and women through the following years. These demographic changes may be due to the aforementioned prioritization of patients with more advanced liver fibrosis at the beginning of the IFN-free era. Such patients were generally older than those with lower severity of the liver disease.

The changes in the percentage of individual HCV genotypes documented in the current analysis were in line with the availability of therapeutic regimens active against specific genotypes. At the beginning of the IFN-free era, genotype-specific options active against GT1 and GT4 were available. In addition, a combination of ASV and DCV, registered exclusively for GT1b-infected patients, was available in Poland.

Therefore, it is understandable that in the first analyzed time intervals, the vast majority of DAA-treated patients were those infected with GT1b. It is important to emphasize that this genotype is dominant in the Polish HCV-infected population, which explains its prevalence also in subsequent time intervals.[31]

At the beginning of the IFN-free era, Polish patients infected with GT3 had access only to a suboptimal regimen of SOF+RBV. Therefore, those with GT3 infection without contraindications to IFN continued to receive IFN-based therapy, including SOF, which was more efficacious.[14]

In 2018, we gained access to pangenotypic regimens in Poland, which are highly effective regardless of the HCV genotype. This fact explains why, since then, there has been an increase in the proportion of patients infected with GT3 among the treated individuals. A similar tendency was also documented in a German HCV-infected population treated with DAA.[20]

The changing profile of patients and therapeutic regimens did not affect the effectiveness of the therapy, which remained at a consistently high and comparable level for all the analyzed periods. The results confirmed the high cure rate of both genotype-specific and pangenotypic regimens, supporting findings of other RWE studies.[32-34] In addition to the suboptimal SOF+RBV option used in GT3-infected patients, lower efficacy was achieved in GT1b-infected patients treated with ASV+DCV, which is consistent with the literature data.[35]

Despite the excellent overall efficacy achieved in the current study, we documented a lower SVR rate in the patients infected with GT3. The introduction of pangenotypic regimens increased the cure rate in this subpopulation but the effectiveness is still worse than for the other genotypes, particularly in individuals with cirrhosis.[36] It should be emphasized that all 15 virologic nonresponders were men, and 6 of them were infected with GT3, 4 of whom were diagnosed with liver cirrhosis and were previous treatment failures. Male sex, prior treatment failure, liver cirrhosis, and GT3 infection are recognized risk factors for failure to respond to DAA therapy, which was confirmed by a recent analysis.[37]

As in other RWE analyses and clinical trials, we observed a favorable safety profile of DAA therapy.[38] It should be noted that the incidence of AEs decreased over time, which was related to less frequent administration of RBV-containing therapy, shortening treatment duration according to labels, and changes in patient characteristics. The most common AEs were weakness / fatigue in all analyzed time intervals, while anemia was documented more frequently in the first analyzed periods, which was associated with the use of RBV.

Our study has several limitations. The retrospective nature of the analysis makes it sensitive to data entry errors, the possible bias of the physician, and underreporting of AEs. The real-world nature of the study may result in a lack of

sufficient rigor during therapy. Moreover, some populations in our analysis are too small to draw reliable conclusions. The data were collected from a single treating center and may not reflect trends in the whole of Poland. However, this limitation is also a strong point of the analysis, as it makes the study the only one of this type that tracks changes in the population of patients treated and followed by the same researchers according to a unified protocol. Another strong point is collecting data from a diverse real-world population, representative of routine practice. Noteworthy is the small proportion of patients lost to the follow-up, which is unique in a retrospective RWE study.

It is also important to note that the analysis includes the COVID-19 pandemic period, which disrupted some previously observed trends, making it more difficult for HCV patients to access diagnosis and therapy.

Conclusion Our results show that the profile of HCV-infected patients evolved from the beginning of the IFN-free era over time. The median age of HCV-infected patients decreased during the consecutive analyzed periods. The patients were less burdened by comorbidities and comedications, more likely to be treatment-naïve, and had less advanced liver disease. The genotype-specific regimens, predominantly used at the beginning of the IFN-free era, were superseded by the pangenotypic regimens, with consistently high effectiveness in all analyzed periods. A lower cure rate was documented in the patients infected with GT3 and those diagnosed with liver cirrhosis irrespective of the time interval. The current analysis also showed a good safety profile of the DAA therapy, which improved over time due to the reduction in RBV use and shortening of the treatment course.

SUPPLEMENTARY MATERIAL

Supplementary material is available at www.mp.pl/paim.

ARTICLE INFORMATION

ACKNOWLEDGMENTS None.

FUNDING Project financed under the program of the Minister of Education and Science called "Regional Initiative of Excellence" in the years 2019–2022, project no. 024/RID/2018/19, for 11 999 000 PLN.

CONTRIBUTION STATEMENT Study design: MB, DZM; data collection: PP, DZM; statistical analysis: MB, KD; data interpretation: MB, KD, DZM; manuscript preparation: MB, KD, DZM; literature search: MB, KD, PP, DZM.

CONFLICT OF INTEREST None declared.

HOW TO CITE Brzdęk M, Dobrowolska K, Pabjan P, Zarębska-Michaluk D. Clinical characteristics and antiviral therapy in patients infected with hepatitis C virus in the interferon-free era. Pol Arch Intern Med. 2022; 132: 16282. doi:10.20452/pamw.16282

REFERENCES

1 World Health Organization. 2022. https://www.who.int/news-room/fact-sheets/detail/hepatitis-c. Accessed March 12, 2022.

2 Westbrook RH, Dusheiko G. Natural history of hepatitis C. J Hepatol. 2014; 61: 58-68.

3 Flisiak R, Pogorzelska J, Berak H, et al. Efficacy of HCV treatment in Poland at the turn of the interferon era - the EpiTer study. Clin Exp Hepatol. 2016; 2: 138-143.

4 Hadziyannis SJ, Sette H, Morgan TR, et al. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med. 2004; 140: 346-355.

5 Janczewska E, Flisiak R, Zarebska-Michaluk D, et al. Effect of peginterferon or ribavirin dosing on efficacy of therapy with telaprevir in treatment-experienced patients with chronic hepatitis C and advanced liver fibrosis: a multicenter cohort study. Medicine (Baltimore). 2015; 94: e1411.

6 Moreno C, Hezode C, Marcellin P, et al. Efficacy and safety of simeprevir with PegIFN/ribavirin in naïve or experienced patients infected with chronic HCV genotype 4. J Hepatol. 2015; 62: 1047-1055.

7 Hézode C, Alric L, Brown A, et al. Randomized controlled trial of the NS5A inhibitor daclatasvir plus pegylated interferon and ribavirin for HCV genotype-4 (COMMAND-4). Antivir Ther. 2015; 21: 195-205.

8 Bhatia HK, Singh H, Grewal N, Natt NK. Sofosbuvir: a novel treatment option for chronic hepatitis C infection. J Pharmacol Pharmacother. 2014; 5: 278-284.

9 Halota W, Flisiak R, Boroń-Kaczmarska A, et al. Recommendations for the treatment of hepatitis C issued by the Polish Group of HCV Experts - 2016. Clin Exp Hepatol. 2016; 2: 27-33.

10 Halota W, Flisiak R, Juszczyk J, et al. Recommendations for the treatment of hepatitis C in 2017. Clin Exp Hepatol. 2017; 3: 47-55.

11 Halota W, Flisiak R, Juszczyk J, et al. Recommendations for the treatment of viral hepatitis C in 2018 by Polish Group of Experts for HCV. Zakażenia XXI Wieku. 2018; 1: 105-113.

12 Halota W, Flisiak R, Juszczyk J, et al. Recommendations for the treatment of viral hepatitis C in 2019 by Polish Group of Experts for HCV. Zakażenia XXI Wieku. 2019; 2: 61-69.

13 Halota W, Flisiak R, Juszczyk J, et al. Recommendations of the Polish Group of Experts for HCV for the treatment of hepatitis C in 2020. Clin Exp Hepatol. 2020; 6: 163-169.

14 Zarębska-Michaluk D, Flisiak R, Jaroszewicz J, et al. Is interferon-based treatment of viral hepatitis C genotype 3 infection still of value in the era of direct-acting antivirals? J Interferon Cytokine Res. 2018; 38: 93-100.

15 Flisiak R, Zarębska-Michaluk D, Jaroszewicz J, et al. Changes in patient profile, treatment effectiveness, and safety during 4 years of access to interferon-free therapy for hepatitis C virus infection. Pol Arch Intern Med. 2020; 130: 163-172.

16 Rammeh S, Khadra HB, Znaidi NS, et al. Inter-observes agreement of Ishak and Metavir scores in histological evaluation of chronic viral hepatitis B and C [in French]. Ann Biol Clin (Paris). 2014; 72: 57-60.

17 European Association for Study of Liver, Asociacion Latinoamericana para el Estudio del Higado. EASL-ALEH Clinical Practice Guidelines: non-invasive tests for evaluation of liver disease severity and prognosis. J Hepatol. 2015; 63: 237-264.

18 Ferraioli G, Tinelli C, Dal Bello B, et al. Accuracy of real-time shear wave elastography for assessing liver fibrosis in chronic hepatitis C: a pilot study. Hepatology. 2012; 56: 2125-2133.

19 Tsoris A, Marlar CA. Use Of The Child Pugh Score In Liver Disease. In: StatPearls. Treasure Island (FL): StatPearls Publishing; March 18, 2022.

20 Hüppe D, Stoehr A, Buggisch P, et al. The changing characteristics of patients infected with chronic hepatitis C virus from 2014 to 2019: real-world data from the German Hepatitis C-Registry (DHC-R). J Viral Hepat. 2021; 28: 1474-1483.

21 Tsai N, Bacon B, Curry M, et al. Changing demographics among populations prescribed HCV treatment, 2013-2017. Am J Manag Care. 2019; 25: 319-323.

22 Flisiak R, Zarębska-Michaluk D, Frankova S, et al. Is elimination of HCV in 2030 realistic in Central Europe? Liver Int Off J Int Assoc Study Liver. 2021; 41 Suppl 1: 56-60.

23 Razavi H, Sanchez Gonzalez Y, Yuen C, Cornberg M. Global timing of hepatitis C virus elimination in high-income countries. Liver Int. 2020; 40: 522-529.

24 Wingrove C, Ferrier L, James C, Wang S. The impact of COVID-19 on hepatitis elimination. Lancet Gastroenterol Hepatol. 2020; 5: 792-794.

25 Yeo YH, Gao X, Wang J, et al. The impact of COVID-19 on the cascade of care of HCV in the US and China. Ann Hepatol. 2022; 27: 100685.

26 Blach S, Kondili LA, Aghemo A, et al. Impact of COVID-19 on global HCV elimination efforts. J Hepatol. 2021; 74: 31-36.

27 Buti M, Domínguez-Hernández R, Casado MA. Impact of the COVID-19 pandemic on HCV elimination in Spain. J Hepatol. 2021; 74: 1246-1248.

28 Berkan-Kawińska A, Piekarska A, Janczewska E, et al. Real-world effectiveness and safety of direct-acting antivirals in patients with cirrhosis and history of hepatic decompensation: Epi-Ter2 Study. Liver Int Off J Int Assoc Study Liver. 2021; 41: 1789-1801.

29 Flisiak R, Zarębska-Michaluk D, Janczewska E, et al. Five-year follow-up of cured HCV patients under real-world interferon-free therapy. Cancers. 2021; 13: 3694.

30 Chirikov VV, Marx SE, Manthena SR, et al. Development of a comprehensive dataset of hepatitis C patients and examination of disease epidemiology in the United States, 2013-2016. Adv Ther. 2018; 35: 1087-1102.

31 Flisiak R, Pogorzelska J, Berak H, et al. Prevalence of HCV genotypes in Poland - the EpiTer study. Clin Exp Hepatol. 2016; 2: 144-148.

32 Lampertico P, Carrión JA, Curry M, et al. Real-world effectiveness and safety of glecaprevir/pibrentasvir for the treatment of patients with chronic HCV infection: a meta-analysis. J Hepatol. 2020; 72: 1112-1121.

33 Backus LI, Belperio PS, Shahoumian TA, et al. Comparative effectiveness of ledipasvir/sofosbuvir ± ribavirin vs. ombitasvir/paritaprevir/ritonavir + dasabuvir ± ribavirin in 6961 genotype 1 patients treated in routine medical practice. Aliment Pharmacol Ther. 2016; 44: 400-410.

34 Mangia A, Milligan S, Khalili M, et al. Global real-world evidence of sofosbuvir/velpatasvir as simple, effective HCV treatment: analysis of 5552 patients from 12 cohorts. Liver Int. 2020; 40: 1841-52.

35 Wang H-L, Lu X, Yang X, Xu N. Effectiveness, and safety of daclatasvir plus asunaprevir for hepatitis C virus genotype 1b: systematic review and meta-analysis. J Gastroenterol Hepatol. 2017; 32: 45-52.

36 Zarębska-Michaluk D, Jaroszewicz J, Parfieniuk-Kowerda A, et al. Effectiveness and safety of pangenotypic regimens in the most difficult to treat population of genotype 3 HCV infected cirrhotics. J Clin Med. 2021; 10: 3280.

37 Janczewska E, Kołek MF, Lorenc B, et al. Factors influencing the failure of interferon-free therapy for chronic hepatitis C: data from the Polish EpiTer-2 cohort study. World J Gastroenterol. 2021; 27: 2177-2192.

38 McGlynn EA, Adams JL, Kramer J, et al. Assessing the safety of direct-acting antiviral agents for hepatitis C. JAMA Netw Open. 2019; 2: e194765.