SPECIAL REPORT

Changes in patient profile, treatment effectiveness, and safety during 4 years of access to interferon-free therapy for hepatitis C virus infection

Robert Flisiak[1], Dorota Zarębska-Michaluk[2], Jerzy Jaroszewicz[3], Beata Lorenc[4], Jakub Klapaczyński[5], Magdalena Tudrujek-Zdunek[6], Marek Sitko[7], Włodzimierz Mazur[8], Ewa Janczewska[9], Paweł Pabjan[2], Dorota Dybowska[10], Iwona Buczyńska[11], Agnieszka Czauż-Andrzejuk[1], Teresa Belica-Wdowik[12], Hanna Berak[13], Rafał Krygier[14], Maciej Piasecki[3], Beata Dobracka[15], Jolanta Citko[16], Anna Piekarska[17], Łukasz Socha[18], Zbigniew Deroń[19], Olga Tronina[20], Łukasz Laurans[18,21], Jolanta Białkowska[22], Krzysztof Tomasiewicz[6], Waldemar Halota[10], Krzysztof Simon[11], Małgorzata Pawłowska[10]

1 Department of Infectious Diseases and Hepatology, Medical University of Białystok, Białystok, Poland
2 Department of Infectious Diseases, Jan Kochanowski University, Kielce, Poland
3 Department of Infectious Diseases in Bytom, Medical University of Silesia, Katowice, Poland
4 Pomeranian Center of Infectious Diseases, Department of Infectious Diseases, Medical University of Gdańsk, Gdańsk, Poland
5 Department of Internal Medicine and Hepatology, Central Clinical Hospital of the Ministry of Internal Affairs and Administration, Warsaw, Poland
6 Department of Infectious Diseases and Hepatology, Medical University of Lublin, Lublin, Poland
7 Department of Infectious and Tropical Diseases, Jagiellonian University Medical College, Kraków, Poland
8 Clinical Department of Infectious Diseases in Chorzów, Medical University of Silesia, Katowice, Poland
9 Department of Basic Medical Sciences in Bytom, Medical University of Silesia, Katowice, Poland
10 Department of Infectious Diseases and Hepatology, Faculty of Medicine, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University, Poland
11 Department of Infectious Diseases and Hepatology, Wrocław Medical University, Wrocław, Poland
12 Regional Center for Diagnosis and Treatment of Viral Hepatitis and Hepatology, John Paul II Hospital, Kraków, Poland
13 Hospital of Infectious Diseases in Warsaw, Warsaw, Poland
14 State University of Applied Sciences in Konin, Konin, Poland
15 Medical Center MedicalSpec, Wrocław, Poland
16 Regional Hospital, Medical Practice of Infections, Olsztyn, Poland
17 Department of Infectious Diseases and Hepatology, Medical University of Lodz, Łódź, Poland
18 Department of Infectious Diseases, Hepatology and Liver Transplantation, Pomeranian Medical University, Szczecin, Poland
19 Department of Infectious Diseases and Hepatology, Biegański Regional Specialist Hospital, Łódź, Poland
20 Department of Transplantation Medicine, Nephrology, and Internal Diseases, Medical University of Warsaw, Warsaw, Poland
21 Outpatient Department, Multidisciplinary Regional Hospital, Gorzów Wielkopolski, Poland
22 Department of Infectious and Liver Diseases, Medical University of Lodz, Łódź, Poland

Correspondence to:
Prof. Robert Flisiak, Department of Infectious Diseases and Hepatology, Medical University of Białystok, ul. Żurawia 14,15-540 Białystok, Poland, phone: +48 85 741 69 21, email: robert.flisiak1@gmail.com
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Introduction Hepatitis C virus (HCV) infection is recognized by the World Health Organization as a major public health problem worldwide that affects 71 million people globally, including over 3 million inhabitants of the European Union.[1-3] The most efficient way to reduce the infection burden, prevent spread of infection, and progression of the disease to liver cirrhosis and hepatocellular carcinoma in individual patients is the identification of those infected and subsequent treatment.[4] Introduction of highly effective and safe direct-acting antivirals (DAA) replaced interferon–based regimens and changed the landscape of HCV treatment.[5-7] However, due to the high cost of treatment with this novel therapy, it was limited to patients with advanced liver disease in a large majority of countries.[8,9]

Direct-acting antiviral–based regimens that are interferon-free for treatment of HCV infection became available in Poland mid-2015. From the beginning, reimbursement had no limitations related to fibrosis or any other factors, which provided a unique possibility to follow changes in patient profile and physicians'

preferences regarding selection of therapeutic options. The only exception were patients infected with HCV genotype 3 (G3), who constituted about 10% of the population, because of the lack of reimbursement for daclatasvir plus sofosbuvir. These patients were treated with sofosbuvir plus ribavirin with or without pegylated interferon alfa until pangenotypic regimens became available in 2018.[10] The first real-world data from studies on ombitasvir / paritaprevir / ritonavir ± dasabuvir and ledipasvir / sofosbuvir in HCV-infected patients, mostly with advanced liver disease, were published in 2016 and demonstrated effectiveness and safety similar to those observed in clinical trials.[11,12]

The EpiTer-2 study was initiated in 2015 to follow epidemiologic changes of HCV infection in Poland and its therapeutic implications related to new treatment options. Initial data from the first year of the study were published in 2018 and focused on the characteristics of the patient population and treatment effectiveness.[13] Further analysis included patients with cirrhosis, those infected with HCV G3, those who did not respond to triple therapy, and those who received retreatment due to failure to respond to genotype-specific DAA before access to pangenotypic regimens.[14-17]

Numerous large real-world studies on the effectiveness of different regimens in various populations were carried out worldwide and published recently.[18-25] However, none of them, except the German Hepatitis C-Registry, documented and analyzed changes in populations of treated patients and their effect on effectiveness and safety of HCV therapy.[25] The aim of the current EpiTer-2 analysis is to follow changes of patient characteristics and HCV treatment in a real-world setting during the initial 4 years of access to interferon-free therapy.

Patients and methods EpiTer-2 is an investigator--initiated study, supported by the Polish Association of Epidemiologists and Infectiologists, which included 22 Polish centers involved in diagnosis and treatment of HCV-infected patients. The EpiTer2 database included 10 152 patients who started treatment for HCV infection in Poland between July 1, 2015 and December 31, 2018 and had an efficacy evaluation report available by July 31, 2019. Data of consecutive patients treated in a therapeutic program reimbursed by the Polish National Health Fund (in Polish, Narodowy Fundusz Zdrowia [NFZ]) were collected retrospectively with a web-based questionnaire. The regimen was selected based on the physician's judgment from available therapeutic options and administered according to the protocol of the NFZ therapeutic program, product characteristics, and recommendations of the Polish Group of Experts for HCV.[26,27] The analysis was carried out by comparison of 3 time intervals—first from 2015 to 2016 (n = 2879), second in 2017 (n = 3349), and third 2018 (n = 3924)—with respect to patients, the disease characteristics, and treatment efficacy determined by sustained virologic response (SVR) defined as undetectable HCV RNA after at least 12 weeks of post-treatment follow-up. Safety outcomes, such as adverse events and laboratory abnormalities were also followed for 12 weeks according to NFZ therapeutic program.

The results are expressed as number and percentage or median and interquartile range. *P* values of less than 0.05 were considered to be significant. Comparisons between groups were performed with nonparametric tests. Sustained virologic response was calculated as intent-to-treat (ITT) analysis and after exclusion of lost to follow-up patients as a modified ITT (mITT). For continuous variables, the significance of difference was calculated by the Kruskal–Wallis test for multigroup comparisons and the Mann–Whitney test for comparisons between 2 groups. For qualitative variables, a *P* value was calculated by the χ^2 test or the Fisher exact test (as appropriate in case of small group size). No corrections for multiple testing in post hoc analyses were applied. Statistical analyses were performed using GraphPad Prism 5.1 (GraphPad Software, Inc., La Jolla, California, United States).

Results The study population was sex-balanced with a small predominance of women, who were older than men. We observed reduction of age between the first and third time interval (TABLE 1). Age distribution demonstrated a biphasic increase of treated patients with the first peak around age 36 to 45 years predominant in men and the second around age 51 to 70 mostly in women. In 2015 to 2016 and in 2017, the second peak was dominant, whereas in 2018, the first peak was higher irrespective of sex (FIGURE 1). The majority of treated patients were overweight or obese (BMI >25), and the proportion of such patients decreased significantly in successive time intervals from 62% to 52% (TABLE 1). Prevalence of comorbidities, including the most frequent, hypertension and diabetes, also decreased from 68.6% in 2015 to 2016 to 59.5% in 2018, and it was accompanied by a tendency for a reduction of the use of concomitant medications (TABLE 1). Genotype 1b infection was the most prevalent, but in successive time intervals decreased significantly from 86.8% to 74.7% and was replaced by an increasing number of patients infected with G1a, G3, and G4 (TABLE 1).

As shown in TABLE 2, severity of liver disease was measured mostly with transient or shear-wave elastography and the role of liver biopsy decreased from 27.7% in 2015 to 2016 to 8.2% in 2018. Advanced liver disease corresponding to the METAVIR score F3 or F4 was noted in about 60% of patients treated in 2015 to 2016, and that number decreased in consecutive time intervals to 45% and 26% (TABLE 2). It was accompanied by some reduction in the number of patients with past or current signs of hepatic decompensation, a decrease of patients with history of hepatocellular carcinoma,

TABLE 1 Characteristics of patients in 3 time intervals

Parameter		2015–2016	2017	2018	*P* value
Number of patients		2879	3349	3924	–
Sex	Women	1473 (51)	1743 (52)	2022 (52)	0.78
	Men	1403 (49)	1606 (48)	1902 (48)	
Age, y, median (IQR)	Both sexes	58 (46–65)	55 (41–63)[a]	49 (38–62)[b]	<0.001
	Women	60 (51–67)	58 (42–65)[a]	53 (38–65)[b]	<0.001
	Men	54 (42–62)	51 (39–61)[a]	46 (37–60)[b]	<0.001
BMI, kg/m^2	<18.5	35 (1.2)	55 (1.6)	73 (1.9)	<0.001
	18.5–25	1007 (35.0)	1335 (39.9)[a]	1721 (43.9)[b]	
	25–30	1245 (43.2)	1281 (38.3)[a]	1399 (35.7)[c]	
	>30	544 (18.9)	570 (17.0)	639 (16.3)	
	No data	48 (1.7)	108 (3.2)[a]	92 (2.3)[c]	
HCV genotype	1a	60 (2.1)	97 (2.9)	180 (4.6)[b]	<0.001
	1b	2499 (86.8)	2640 (78.8)[a]	2931 (74.7)[b]	
	1 (no subgenotyping)	36 (1.3)	89 (2.7)[a]	73 (1.9)[c]	
	2	3 (0.1)	2 (0.1)	8 (0.2)	
	3	198 (6.9)	356 (10.6)[a]	510 (13.0)[c]	
	4	83 (2.9)	165 (4.9)[a]	220 (5.6)	
	5	0	0	0	
	6	0	0	2 (0.1)	
Comorbidities	Any comorbidity	1976 (68.6)	2268 (67.7)	2335 (59.5)[b]	<0.001
	Hypertension	1128 (39.2)	1210 (36.1)[d]	1191 (30.3)[b]	<0.001
	Diabetes	482 (16.7)	461 (13.8)[a]	384 (9.8)[b]	<0.001
	Renal insufficiency	121 (4.2)	204 (6.1)[d]	122 (3.1)[b]	<0.001
	Autoimmune disease	79 (2.7)	59 (1.8)[d]	85 (2.2)	0.03
	Non-HCC tumors	58 (2.0)	57 (1.7)	72 (1.8)	0.66
	Other	1369 (48.6)	1764 (52.7)[a]	1739 (44.3)[b]	<0.001
Concomitant medications		1859 (64.6)	2131 (63.6)	2266 (57.7)[b]	<0.001

Data are presented as number (percentage) unless otherwise indicated.

a 2015–2016 vs 2017, P <0.001

b 2017 vs 2018, P <0.001

c 2017 vs 2018, P <0.05

d 2015–2016 vs 2017, P <0.05

Abbreviations: BMI, body mass index; HCC, hepatocellular carcinoma; HCV, hepatitis C virus

and an increasing proportion of patients with the Model for End-Stage Liver Disease (MELD) score below 15 and classified as Child-Pugh class A. Additionally, the number of patients who had undergone liver transplantation decreased from 100 in 2015–2016 to 3 in 2018 (TABLE 2). As shown in TABLE 2, there was a reduction of cryoglobulinemia frequency, but there were no changes in prevalence of other extrahepatic manifestations and hepatitis B virus coinfections. On the other hand, we observed an increase of HIV prevalence among all treated patients from 1.4% to 7.3%.

In 2015 to 2016, 53% of patients were retreated due to failure or discontinuation of previous therapy, whereas in 2017 and 2018, the proportion of these patients decreased significantly to 34% and 14%, respectively (TABLE 3). Among retreated patients in all time intervals, those who failed interferon-based regimens were predominant. However, in 2018, 77 retreated nonresponders to interferon-free regimens were registered, compared with 27 in 2015–2016 and 2017 (TABLE 3). In 2015 to 2016, almost two-thirds of patients received ombitasvir/paritaprevir/ritonavir ± dasabuvir ± ribavirin, but in subsequent time intervals, this regimen was replaced in part by ledipasvir/sofosbuvir ± ribavirin and grazoprevir/elbasvir ± ribavirin (TABLE 3). Therapeutic options based on sofosbuvir, including pegylated interferon–containing therapy administered to G3-infected patients in 2015–2016 and 2017, were replaced by pangenotypic regimens in 2018. About 20% of patients who started therapy in 2018 were treated with either velpatasvir/sofosbuvir ± ribavirin or glecaprevir/pibrentasvir.

Effectiveness of treatment in the whole population, measured as ITT analysis, was 95%, but in the mITT it was 97%, and similar SVR rates were

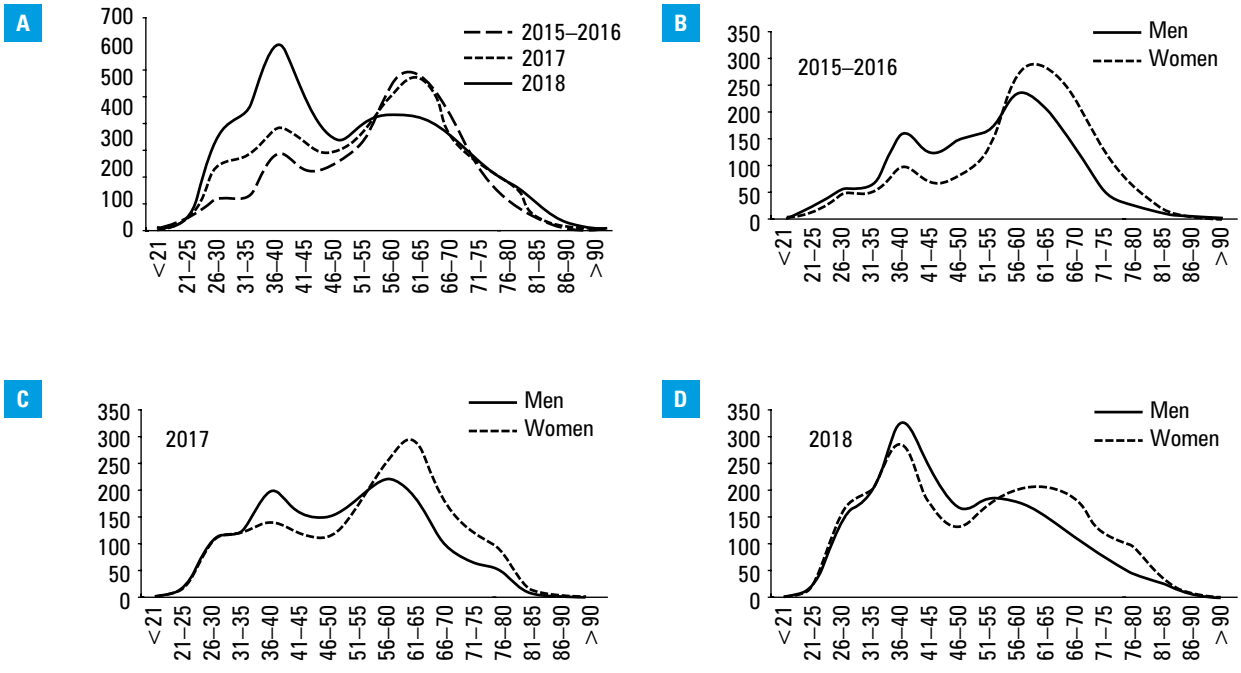


FIGURE 1 Age distribution in all patients treated in 3 time intervals (A) and in women and men in: 2015–2016 (B), 2017 (C), 2018 (D)

noted in all time intervals. As shown in TABLE 4, similar effectiveness of 98% (mITT) was observed in patients treated with the most frequently administered regimens of ombitasvir / paritaprevir / ritonavir ± dasabuvir ± ribavirin, ledipasvir / sofosbuvir ± ribavirin, and grazoprevir / elbasvir ± ribavirin, as well as pangenotypic therapy with glecaprevir / pibrentasvir. The most stable effectiveness of 98% (mITT) across successive years was demonstrated in the biggest group of patients infected with G1b. On the other hand, the lowest SVR rate was observed among those infected with G3, but effectiveness improved significantly (P = 0.004) from 87% to 94% (FIGURE 2). As shown in FIGURE 3, the SVR rate was similar in patients without cirrhosis irrespective of the time interval (97%–99%). In patients with cirrhosis, it was 96% in 2015 to 2016 and decreased to 94%, but the difference was not significant (FIGURE 3).

Analysis of the safety profile demonstrated a reduction in the prevalence of adverse events from 32.5% in 2015 to 2016 to 18.1% in 2018. The same tendency was observed regarding serious adverse events, deaths, and treatment discontinuations (TABLE 5). The most frequently reported adverse events were weakness or fatigue, headache, and pruritus. Both adverse events and laboratory abnormalities were infrequent and mild (TABLE 5). Decreasing prevalence of safety issues in successive time intervals was accompanied by reduced frequency of regimens containing ribavirin (TABLE 3). This tendency was observed mostly in patients receiving interferon-free regimens, which demonstrated decline of ribavirin use from 44.6% (2015–2016) to 10.6% (2018).

Discussion About 28 thousand patients were treated for HCV infection in more than 60 Polish centers during the analyzed time interval, which started in mid-2015 with the introduction of the NFZ therapeutic program for viral hepatitis C providing reimbursement of interferon-free regimens without any fibrosis limitations. Since the Epi-Ter-2 database includes 10 152 patients (36% of the whole population) from 22 treating centers, we can assume that sample is representative for the country. Due to the lack of official NFZ reports on patients' characteristics, treatment effectiveness and its safety, these data are the only source of information on changes in the population of patients infected with HCV and treated in Poland. They are particularly useful to predict HCV elimination, which according to the recent estimations will not be possible without annual screening of 2.5 to 3 million inhabitants and treatment of 12 thousand of those diagnosed.[28] Previously published analysis carried out in 2013 to 2015 demonstrated G1b and G3 prevalence of 82% and 11%, respectively.[29] The current study showed a decrease of G1b frequency to 75% and its increase regarding other genotypes between 2015 and 2018, which is similar to the findings of Huppe et al[25] in a German population. It can be explained by access to highly effective interferon-free genotype specific regimens administered mostly to G1-infected patients. On the other hand, there was no reimbursement of the daclatasvir plus sofosbuvir regimen for G3, so the available options (sofosbuvir plus pegylated interferon plus ribavirin and sofosbuvir plus ribavirin) in this population were suboptimal.

The lower age of treated patients between the first and third time interval in our study was similar to the Hepatitis C-Registry population.[25] The irregularity in the age distribution noted after the first year of the study and visible in the

TABLE 2 Characteristics of liver disease in 3 time intervals

Parameter		2015–2016	2017	2018	*P* value
Liver fibrosis assessment	Biopsy	798 (27.7)	599 (17.9)[a]	322 (8.2)[b]	<0.001
	TE	1613 (56)	2023 (60.4)[a]	2509 (63.9)[c]	
	SWE	394 (13.7)	657 (19.6)[a]	1080 (27.5)[b]	
	ARFI	7 (0.2)	21 (0.6)[d]	2 (0.1)[b]	
	No assessment	67 (2.3)	49 (1.5)[d]	11 (0.3)[b]	
Fibrosis (METAVIR score)	F0	13 (0.5)	28 (0.8)	122 (3.1)[b]	<0.001
	F1	611 (21.2)	1109 (33.1)[a]	1890 (48.2)[b]	
	F2	388 (13.5)	644 (19.2)[a]	874 (22.3)[c]	
	F3	460 (16)	640 (19.1)[d]	441 (11.2)[b]	
	F4	1254 (43.6)	870 (26)[a]	581 (14.8)[b]	
	Unknown	153 (5.3)	58 (1.7)[a]	16 (0.4)[b]	
History of hepatic decompensation	Ascites	164 (5.7)	86 (3)[a]	72 (2.2)[c]	<0.001
	Hepatic encephalopathy	56 (1.9)	21 (1)[a]	22 (1)	<0.001
Documented esophageal varices		519 (18)	294 (8.8)[a]	141 (3.6)[b]	<0.001
Hepatic decompensation at baseline	Moderate ascites (responded to diuretics)	59 (2.0)	36 (1.1)	35 (0.9)	0.25
	Tense ascites (did not respond to diuretics)	4 (0.1)	0	3 (0.1)	
	Hepatic encephalopathy, grade 1–2	38 (1.3)	17 (0.5)	12 (0.3)	0.69
	Hepatic encephalopathy, grade 3–4	1 (0.03)	0	0	
MELD	<15	2578 (89.5)	3123 (93.3)[a]	3781 (96.4)[b]	<0.001
	15–18	76 (2.5)	55 (1.6)[d]	65 (1.7)	
	19–20	29 (1)	55 (1.6)[d]	28 (0.7)[b]	
	>20	25 (0.9)	21 (0.6)	31 (0.8)	
	No data	171 (5.9)	95 (2.8)[a]	19 (0.5)[b]	
Child-Pugh class	A	2592 (90)	3150 (94.1)[a]	3828 (97.6)[b]	<0.001
	B	150 (5.6)	98 (2.9)[a]	74 (1.9)[#]	
	C	12 (0.4)	1 (0.03)[d]	3 (0.08)	
	No data	115 (4)	100 (3)[d]	19 (0.5)[b]	
History of HCC		91 (3.2)	60 (1.8)[a]	28 (0.7)[b]	<0.001
History of liver transplantation		100 (3.5)	42 (1.3)[a]	3 (0.08)[b]	<0.001
Extrahepatic manifestations of HCV infection	Cryoglobulinemia	197 (6.8)	227 (6.8)	177 (4.5)[b]	0.005
	Thyroid abnormalities with antithyroid antibodies	39 (1.4)	30 (0.9)	38 (1)[c]	
	Thrombocytopenia with or without cirrhosis and splenomegaly	15 (0.5)	18 (0.5)	37 (0.9)	
	Other	24 (0.8)	24 (0.7)	24 (0.6)	
HIV coinfections		41 (1.4)	132 (3.9)[a]	287 (7.3)[b]	<0.001
HBV coinfections	Reported coinfection	288 (10)	538 (16.1)[a]	523 (13.3)[c]	<0.001
	HBV DNA (+)	11 (0.4)	22 (0.7)	19 (0.5)	0.3
	HBsAg (+)	28 (1)	42 (1.3)	41 (1)	0.53
	Anti-HBc total (+)	269 (9.3)	516 (15.4)[a]	514 (13.1)[c]	<0.001

Data are presented as number (percentage).

a 2015–2016 vs 2017, $P < 0.001$

b 2017 vs 2018, $P < 0.001$

c 2017 vs 2018, $P < 0.05$

d 2015–2016 vs 2017, $P < 0.05$

Abbreviations: anti-HBc, antibodies against hepatitis B core antigen; ARFI, acoustic radiation force impulse; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; MELD, Model for End-Stage Liver Disease; SWE, shear-wave elastography; TE, transient elastography; others, see **TABLE 1**

TABLE 3 Treatment characteristics in 3 time intervals (table footnotes on the next page)

Parameter	2015–2016		2017		2018		*P* value
Treatment history							
Naïve	1338 (46.5)		2226 (66.5)[a]		3346 (85.3)[b]		<0.001
Relapse	405 (14.5)		322 (9.6)[a]		211 (5.4)[b]		
Null response	571 (19.8)		361 (10.8)[a]		187 (4.8)[b]		
Discontinuation for safety reasons	181 (6.3)		142 (4.2)[a]		61 (1.6)[b]		
Nonresponse – type unknown	373 (12.9)		280 (8.4)[a]		107 (2.7)[b]		
Unknown history	13 (0.5)		18 (0.5)		12 (0.3)		
Previous regimen in patients with treatment failure							
Number of patients with treatment failure	1530		1105		566		–
PegIFN + RBV	1091 (71.3)		891 (80.6)[a]		416 (73.5)[c]		<0.001
TVR + PegIFN + RBV	181 (11.8)		49 (4.4)[a]		4 (0.7)[b]		
BOC + PegIFN + RBV	108 (7.1)		30 (2.7)[a]		10 (1.8)		
IFNnat + RBV	71 (4.6)		29 (2.6)[d]		2 (0.4)[b]		
IFNalfa + RBV	29 (1.9)		45 (4.1)[d]		6 (1.1)[b]		
SMV + PegIFN + RBV	26 (1.7)		34 (3.1)[d]		15 (2.7)		
SOF + PegIFN + RBV	4 (0.3)		3 (0.3)		18 (3.2)[b]		
IFN-free	10 (0.7)		17 (1.5)[d]		77 (13.6)[b]		
Other IFN-containing and unknown	10 (0.7)		7 (0.6)		18 (3.2)[b]		
Current treatment regimen							
OBV/PTV/r + DSV, 8 weeks	2 (0.07)	1852 (64.3)	221 (6.6)	1486[a] (44.4)	236 (6)	712[b] (18.1)	<0.001
OBV/PTV/r + DSV, 12 weeks	1029 (35.7)		1021 (30.5)		364 (9.3)		
OBV/PTV/r + DSV + RBV, 12 weeks	711 (24.7)		112 (3.3)		37 (0.9)		
OBV/PTV/r + DSV + RBV, 24 weeks	34 (1.2)		22 (0.7)		0		
OBV/PTV/r + RBV, 12 weeks	42 (1.5)		103 (3.1)		75 (1.9)		
OBV/PTV/r + RBV, 24 weeks	34 (1.2)		7 (0.2)		0		
LDV/SOF, 8 weeks	59 (2.1)	692 (24)	179 (5.3)	1027[a] (30.7)	357 (9.1)	1080[c] (27.5)	<0.001
LDV/SOF, 12 weeks	193 (6.7)		483 (14.5)		568 (14.5)		
LDV/SOF, 24 weeks	76 (2.6)		53 (1.6)		25 (0.6)		
LDV/SOF + RBV, 12 weeks	317 (11.0)		299 (8.9)		126 (3.2)		
LDV/SOF + RBV, 24 weeks	47 (1.6)		12 (0.4)		4 (0.1)		
SOF + RBV, 12 weeks	1 (0.03)	99 (3.4)	1 (0.03)	235[a] (7)	6 (0.2)	73[b] (1.9)	<0.001
SOF + RBV, 24 weeks	74 (2.6)		199 (5.9)		56 (1.4)		
SOF + DCV ± RBV, 24 weeks	12 (0.4)		29 (0.9)		11 (0.3)		
SOF + SMV ± RBV, 12 weeks	10 (0.4)		0		0		
GZR/EBR, 12 weeks	0	0	394 (11.8)	410 (12.2)	1165 (29.7)	1199[b] (30.6)	<0.001
GZR/EBR +vRBV, 16 weeks	0		16 (0.5)		34 (0.9)		
SOF/VEL, 12 weeks	2 (0.07)	2 (0.07)	6 (0.2)	6 (0.2)	350 (8.9)	417[b] (10.6)	<0.001
SOF/VEL + RBV, 12 weeks	0		0		43 (1.1)		
SOF/VEL ± RBV, 24 weeks	0		0		24 (0.6)		
GLE/PIB, 8 weeks	0	0	3 (0.1)	3 (0.1)	254 (6.5)	378[b] (9.6)	<0.001
GLE/PIB, 12 weeks	0		0		97 (2.5)		
GLE/PIB, 16 weeks	0		0		27 (0.7)		
DCV + SMV + RBV	3 (0.1)	96 (3.3)	0	41[a] (1.2)	0	0	<0.001
DCV + ASV, 24 weeks	93 (3.2)		41 (1.2)		0		
SOF + PegIFN + RBV, 12 weeks	101 (3.5)	130 (4.5)	134 (4)	140 (4.2)	63 (1.6)	63[b] (1.6)	<0.001
TVR + PegIFN + RBV	3 (0.1)		0		0		
SMV + PegIFN + RBV	7 (0.2)		2 (0.1)		0		
PegIFN + RBV, 24 weeks	19 (0.7)		4 (0.12)		0		
Other	10 (0.4)	10 (0.3)	8 (0.2)	8 (0.2)	2 (0.05)	2 (0.05)	0.02
RBV-containing therapies	1417 (49.2)		928 (27.7)[a]		477 (12.2)[b]		<0.001

TABLE 3 Treatment characteristics in 3 time intervals (footnotes to the table on the previous page)

Data are presented as number (percentage).

a 2015–2016 vs 2017, $P < 0.001$

b 2017 vs 2018, $P < 0.001$

c 2017 vs 2018, $P < 0.05$

d 2015–2016 vs 2017, $P < 0.05$

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

TABLE 4 Treatment effectiveness according to regimen, calculated as ITT and mITT analysis, which included all therapeutic options administered to at least 10 patients

Regimen		SVR, ITT[a], % (n/N)	SVR, mITT[b], % (n/N)
All regimens		95 (9614/10152)	97 (9614/9883)
OBV/PTV/r ± DSV ± RBV			
Total		97 (1918/4052)	98 (3918/3986)
OBV/PTV/r + DSV	8 weeks	96 (442/459)	97 (442/457)
	12 weeks	97 (2348/2415)	99 (2348/2378)
OBV/PTV/r + DSV + RBV	12 weeks	96 (824/860)	98 (824/842)
	24 weeks	91 (52/57)	98 (52/53)
OBV/PTV/r + RBV	12 weeks	96 (212/220)	98 (212/216)
	24 weeks	98 (40/41)	100 (40/40)
LDV/SOF ± RBV			
Total		95 (2680/2811)	98 (2680/2730)
LDV/SOF	8 weeks	97 (577/595)	99 (577/583)
	12 weeks	96 (1201/1254)	98 (1201/1220)
	24 weeks	92 (141/154)	99 (141/143)
LDV/SOF + RBV	12 weeks	94 (702/745)	97 (702/727)
	24 weeks	94 (59/63)	95 (59/62)
GZR/EBR ± RBV			
Total		95 (1542/1616)	98 (1542/1570)
GZR/EBR ± RBV	12 weeks	95 (1489/1560)	98 (1489/1517)
	16 weeks	95 (53/56)	100 (53/53)
VEL/SOF ± RBV			
Total		88 (376/425)	95 (376/397)
VEL/SOF	12 weeks	91 (323/356)	98 (323/331)
VEL/SOF + RBV	12 weeks	76 (34/45)	76 (34/45)
	24 weeks	79 (19/24)	90 (19/21)
GLE/PIB			
Total		96 (364/380)	98 (364/371)
GLE/PIB	8 weeks	96 (244/255)	98 (244/249)
	12 weeks	97 (94/97)	100 (94/94)
	16 weeks	93 (26/28)	93 (26/28)
Other regimens			
DCV + ASV, 24 weeks		88 (119/135)	90 (119/132)
SOF + RBV, 24 weeks		79 (364/463)	85 (364/427)
SOF + DCV ± RBV, 24 weeks		91 (39/43)	98 (39/40)
SOF + SMV ± RBV, 12 weeks		90 (9/10)	90 (9/10)
SOF + PegIFN + RBV, 12 weeks		91 (395/435)	93 (395/427)

a Analysis included all patients receiving at least 1 dose of the treatment

b Analysis excluded patients with missing data of sustained virologic response (12 or 24 weeks after treatment completion)

Abbreviations: ITT, intent-to-treat analysis; mITT, modified intent-to-treat analysis; others, see **TABLE 3**

FIGURE 2 Sustained virologic response rates according to genotypes in 3 time intervals, calculated according to modified intent-to-treat analysis (patients lost to follow-up excluded)

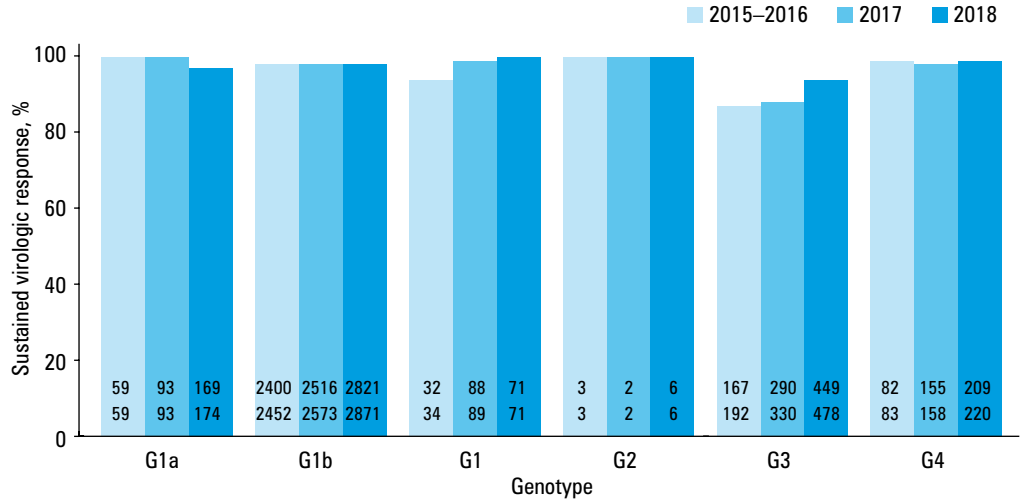
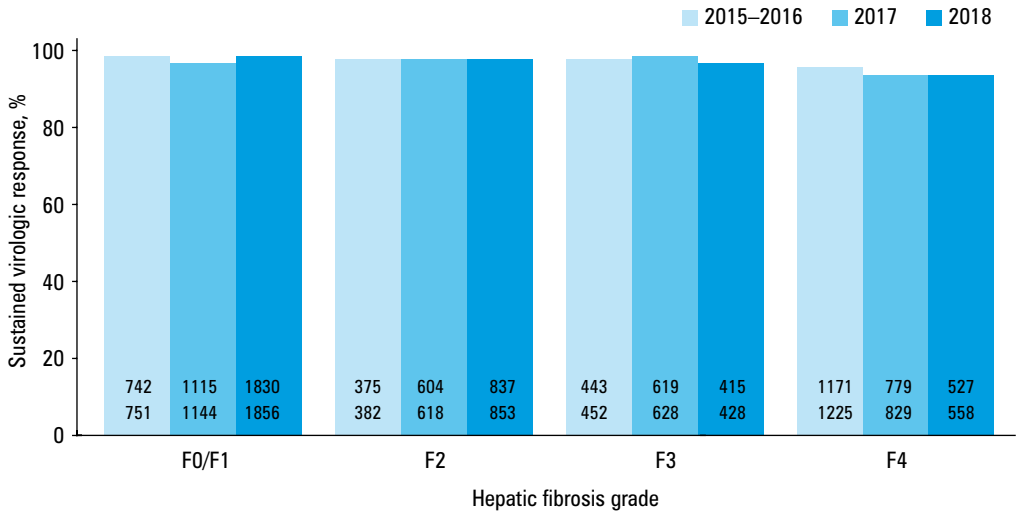


FIGURE 3 Sustained virologic response rates according to grade of hepatic fibrosis (METAVIR score) in 3 time intervals, calculated according to modified intent-to-treat analysis (patients lost to follow-up excluded)



2-peak pattern, with predominant age group between 56 and 65 years in the second peak, was currently confirmed and seems to be specific for the Polish population.[13] However, in 2018, the first peak population aged between 36 and 45 years became dominant and the majority of patients in this group were men. Interestingly, according to the recently published data, the majority of HIV-coinfected patients in Poland are men of this age group, therefore, a conclusion can be made that, at least in part, male sex and drug use at the end of the 20th century could be responsible for the higher number of those treated aged 36 to 45 years.[30] The reason of younger age in 2018 is priority given at the beginning of DAA era to patients with more advanced liver disease, who were usually older. Until 2018, treating centers enrolled patients from waiting lists, so age distribution and disease advancement were not affected by the national screening program, which will hopefully start in 2020. There were no changes in access to treatment for drug users, so it also does not affect age distribution. Generally speaking, patients receiving treatment for HCV infection during the analyzed time interval became healthier, which was demonstrated through the reduced proportion of advanced liver disease, as well as decrease of comorbidities and comedication. Despite a decline in comorbidities frequency, there is stable prevalence of autoimmune diseases which can still be activated even during interferon-free therapy.[31] Compared with previous studies carried out in Poland before 2018, the most visible is the decline of the proportion of patients with cirrhosis, particularly those with decompensation, hepatocellular carcinoma, or liver transplantation history.[11-15] This tendency is what we expected from efficient HCV therapy—to cure patients in early phase of the infection and prevent progression to liver cirrhosis and hepatocellular carcinoma. As demonstrated previously, treatment of patients with advanced liver disease is sometimes introduced too late to reverse development of hepatocellular carcinoma.[32]

In 2015–2016, the majority of patients were treatment-experienced, whereas in 2018, previous therapy was reported only in 15%. In all 3 time intervals, a large majority (71%–81%) of retreated patients failed dual therapy with pegylated interferon plus ribavirin. However, the proportion of previous failures for interferon-free regimens increased from 0.7% in 2015 to 2016 to 13.6% in 2018. Patients were treated according to the NFZ protocol that is based on drugs' characteristics and recommendations of the Polish Group

TABLE 5 The most frequent (>1%) adverse events, laboratory abnormalities, and other treatment safety measures in 3 time intervals

Parameter	2015–2016 (n = 2879)	2017 (n = 3349)	2018 (n = 3924)	*P* value
Adverse events	937 (32.5)	756 (22.6)[a]	710 (18.1)[b]	<0.001
Serious adverse events	89 (3.1)	21 (0.6)[a]	38 (1)	<0.001
Deaths	23 (0.8)	14 (0.4)	17 (0.4)	<0.001
Treatment discontinuations	68 (2.4)	43 (1.3)[c]	29 (0.8)[d]	<0.001
Most frequent adverse events (>1%)				
Weakness/fatigue	442 (15.4)	345 (10.3)[a]	319 (8.1)[d]	<0.001
Headache	99 (3.4)	97 (2.9)	124 (3.2)	0.47
Pruritus	108 (3.8)	85 (2.5)[c]	47 (1.2)[b]	<0.001
Sleep disorders	90 (3.2)	71 (2.1)[c]	81 (2.1)	0.009
Myalgia/arthralgia	40 (1.4)	73 (2.2)	66 (1.7)	0.05
Nausea	62 (2.2)	45 (1.3)[c]	43 (1.1)	0.001
Abdominal pain	44 (1.5)	39 (1.2)	46 (1.2)	0.34
Skin lesions	49 (1.7)	35 (1)[c]	27 (0.7)	<0.001
Laboratory abnormalities				
Anemia, G ≥2	174 (6)	144 (4.3)[c]	59 (1.5)[b]	<0.001
Neutropenia, G ≥2	9 (0.3)	10 (0.3)	4 (0.1)	0.11
Thrombocytopenia, G ≥2	8 (0.3)	15 (0.5)	6 (0.15)	0.06
Hyperbilirubinemia, G ≥2	90 (3.1)	49 (1.5)[a]	15 (0.4)[a]	<0.001
Elevation of aminotransferases, G ≥2	25 (0.9)	9 (0.3)[c]	4 (0.1)	<0.001

Data are presented as number (percentage).

a 2015–2016 vs 2017, *P* <0.001

b 2017 vs 2018, *P* <0.001

c 2015–2016 vs 2017, *P* <0.05

d 2017 vs 2018, *P* <0.05

of Experts for HCV.[26,27] Selection of the regimen for a particular patient among available therapeutic options was based on the physician's judgment. In 2015 to 2016, almost two-thirds of patients were treated with ombitasvir / paritaprevir / ritonavir ± dasabuvir ± ribavirin, but in subsequent time intervals, prescribed regimens became much more diverse, which was a consequence of competition and finally availability of pangenotypic regimens at the end of 2018.

Effectiveness of treatment with the most frequently administered regimens in the analyzed time interval was very high and similar to that demonstrated in other large real-world experience studies.[18-25] The only surprising exception was the relatively low SVR rate after treatment with sofosbuvir / velpatasvir, which improved after exclusion of patients lost to follow-up. This phenomenon needs further analysis with a greater number of patients on this regimen included in the future. On the other hand, we observed, similar to previous publications, a relatively high response rate to the last available interferon-based regimen, sofosbuvir plus pegylated interferon plus ribavirin, which was dominant in Poland for G3 infections until mid-2018.[14,33,34] Effectiveness of treatment was stable across genotypes and fibrosis except in patients infected with G3, which was lower than in those infected with other genotypes. However, it seems that access to pangenotypic regimens improved the SVR rate in this population in 2018. Interestingly, overall effectiveness of treatment analyzed in 2612 patients with cirrhosis was reduced to 95%. Safety profile of the therapies improved in subsequent time intervals, which was the result of changes in patient characteristics, shortening of treatment, and reduced use of ribavirin responsible for a number of adverse events, particularly in the first time interval. A decrease in the frequency of weakness or fatigue, pruritus, anemia, and hyperbilirubinemia is a result of less frequent ribavirin administration.

In conclusion, data collected in this long-term study carried out in a real-world settings demonstrate significant changes in characteristics of treated patients compared with the initial time interval when interferon-free regimens became available. These patients are younger, mostly treatment naïve, have less advanced disease, and fewer comorbidities and comedications. Together with shortening of treatment and ribavirin elimination, it resulted in improvement of safety. On the other hand, changing regimens during the 4-year interval did not influence the effectiveness, which remained at the level of 97%.

ARTICLE INFORMATION

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