



Decade of optimizing therapy with direct-acting antiviral drugs and the changing profile of patients with chronic hepatitis C

Michał Brzdęk, Dorota Zarębska-Michaluk, Federica Invernizzi, Marta Cilla, Krystyna Dobrowolska, Robert Flisiak

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Michał Brzdęk, Krystyna Dobrowolska, Collegium Medicum, Jan Kochanowski University, Kielce 25-516, Poland

Dorota Zarębska-Michaluk, Department of Infectious Diseases, Jan Kochanowski University, Kielce 25-516, Poland

Federica Invernizzi, Marta Cilla, Center for Liver Disease, Division of Internal Medicine and Hepatology, IRCCS Ospedale San Raffaele, Milan 20-132, Italy

Robert Flisiak, Department of Infectious Diseases and Hepatology, Medical University of Białystok, Białystok 15-540, Poland

Corresponding author: Dorota Zarębska-Michaluk, PhD, Professor, Department of Infectious Diseases, Jan Kochanowski University, Radiowa 7, Kielce 25-516, Poland. dorota1010@tlen.pl

Abstract

Chronic infection with the hepatitis C virus (HCV) remains a major health problem affecting approximately 58 million people worldwide. In the era of interferon (IFN)-based regimens, patients particularly infected with genotypes 1 and 4 achieved a low response rate. The implementation of direct-acting antivirals changed the landscape of HCV treatment. The increase in effectiveness provided us with the hope of eliminating HCV as a significant public threat by 2030. In the following years, there was an observed improvement in the treatment of HCV with genotype-specific regimens and highly effective pangenotypic options that are the most recent stage of the revolution. The optimization of therapy was accompanied by changes in the patient profile from the beginning of the IFN-free era over time. Patients treated with antiviral therapies were younger in successive periods, less burdened with comorbidities and comedications, more frequently treatment-naïve and had less advanced liver disease. Before the IFN-free era, specific subpopulations such as patients with HCV/HIV coinfection, those with a history of previous treatment, patients with renal impairment or with cirrhosis had lower chances for a virologic response. Currently, these populations should no longer be considered difficult to treat. Despite the high effectiveness of HCV therapy, there is a small percentage of patients with treatment failure. However, they can be effectively retreated with pangenotypic rescue regimens.

Key Words: Hepatitis C virus; Interferon; Direct-acting antiviral; Epidemiology; Chronic

Core Tip: A decade ago direct-acting antiviral drugs were introduced and have greatly improved the effectiveness of treatment for patients with hepatitis C virus infection. The new drugs have increased the chances of eliminating hepatitis C virus infection as a significant public threat. This paper described changes in the therapeutic options administered over the past decade and documented the changing patient profile over the years in the interferon-free era. Special populations of difficult-to-treat patients in the interferon era currently not meeting this definition are highlighted.

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INTRODUCTION

Chronic infection with hepatitis C virus (HCV) is one of the leading causes of liver disease in the world. According to the most recent estimates from the World Health Organization (WHO), 58 million people are living with chronic hepatitis C (CHC) worldwide, with the annual number of new infections reaching 1.5 million[1]. About 20% of them are at risk of developing liver cirrhosis, eventually leading to organ failure and hepatocellular carcinoma[2]. These most severe complications of the disease are the cause of death of approximately 290000 people a year. There is no effective vaccine against HCV, but currently available direct-acting antivirals (DAA) can cure more than 95% of people infected with hepatitis C regardless of the genotype (GT).

To date, six major HCV GTs have been identified that differ in more than 35% of the genome sequence[3]. The most common of these worldwide is GT1, considered the most difficult to treat in the era of interferon (IFN)-based therapies. However, this was the first GT in which very high efficacy was achieved with GT-specific therapies at the beginning of the DAA era[4]. Further evolution of antiviral therapy has led to the availability of regimens that are highly effective in infection with any HCV GT and at any stage of liver disease, including decompensated liver cirrhosis[5]. In addition to increased efficacy, safety parameters have improved, and antiviral therapy has become shorter and now lasts 8 or 12 wk in the vast majority of patients[6]. There was also a simplification of regimens by dropping the addition of ribavirin (RBV), which also translated into improved tolerability. Optimization of antiviral therapy has set the groundwork for achieving the WHO's goal of eliminating HCV infection as a public health threat by 2030. The goal to realize this target remains the diagnosis of infection in patients who are unaware of it.

CHANGES IN THERAPEUTIC REGIMENS

IFN-based therapy

Regimens without DAA: The era of IFN in the treatment of HCV infection began in 1986, even before the identification of the virus, which was then known as non-A, non-B hepatitis virus. Hoofnagle *et al*[7] documented a reduction in transaminase activity as a result of IFN α 2b therapy. Despite the beneficial effect of reducing disease activity, the initial responses to treatment were transient[8]. In subsequent years, other investigators reported that the decline was related to viral clearance or a decrease in serum HCV RNA[9]. Sustained virological response (SVR) after 24-wk monotherapy with recombinant IFN ranged from 3%-6%, and IFN administered for 48 wk resulted in 13%-19% efficacy[10,11]. Adding RBV to IFN improved treatment efficacy to about 40%[10-13].

The next milestone in the antiviral treatment was the introduction of two forms of long-acting pegylated IFN (pegIFN), alfa-2a and alfa-2b, which were used once a week. This change was one of the key elements in improving treatment adherence and greater efficacy of antiviral therapy[14,15]. In randomized multicenter trials, the SVR rate with pegIFN monotherapy ranged from 15% to 39%[16,17], and the addition of RBV to the regimen increased efficacy to about 50%[15,18]. HCV GTs has been identified as the most important independent predictor of response to pegIFN + RBV treatment.

The prospective PROPHECY study involving 7163 patients treated with pegIFN + RBV for 48 wk showed better efficacy rates of 71.4% and 60.6% in patients with GT2 and GT3 infections, respectively, compared to patients with GT1 (41.8%) and GT4 (41%) infections. The higher efficacy of therapy was also observed in patients without advanced liver fibrosis or cirrhosis[19]. The most important predictor of response to therapy regardless of HCV GT was undetectable HCV RNA at week 4 of therapy, defined as the rapid virological response as proven by a retrospective study involving 1383 patients[20]. These findings allowed the reduction of the length of treatment to less than 24 wk in GT2- and GT3-infected patients who achieved rapid virological response without a significant decrease in efficacy compared to those with detectable HCV RNA after 4 wk of treatment who required treatment for 24 wk[21]. In addition to virologic

response at week 4, treatment length was determined by the response at week 12; GT1-infected patients with detectable serum HCV RNA after 12 wk of treatment benefited from extending treatment to 72 wk[22,23].

The efficacy of IFN-containing regimens was limited by safety issues; adverse events of therapy were frequent and led to treatment discontinuation in 5%-16% of cases[15,24]. Fatigue, headache, fever, malaise, myalgia, neutropenia and thrombocytopenia were reported as the most common adverse events[25]. The main side effect associated with RBV use resulting in its dose reduction in 20% of patients was hemolytic anemia[18].

Regimens with DAA: The introduction of the protease inhibitors telaprevir (TVR) and boceprevir in 2011 launched the era of the first DAAs for the treatment of HCV infection[26,27]. Initially, the new drugs were registered for use with pegIFN + RBV only in patients with GT1 infection. Cure rates following triple therapy increased to about 70% compared to previously used regimens containing only pegIFN + RBV[28]. Results from the randomized, double-blind, placebo-controlled ADVANCE trial evaluating a triple regimen with TVR in treatment-naïve GT1-infected patients showed that therapy could be shortened to 24 wk in most without reducing efficacy[29].

Among patients after previous treatment failure assessed in the randomized phase 3 REALIZE trial, patients with prior relapse achieved SVR rates of 83%-88% following treatment with pegIFN + RBV + TVR, while this was only 30% for null responders[30].

The most difficult population to treat with a triple regimen containing first-generation protease inhibitors, TVR or boceprevir, was the population of treatment-experienced patients with liver cirrhosis due to very low efficacy and a poor safety profile[31-33].

Registration of new DAAs has broadened the spectrum of clinical use of triple-drug regimens. The protease inhibitor simeprevir and the non-structural protein 5A (NS5A) inhibitor daclatasvir (DCV) combined with pegIFN + RBV could be used in GT1-infected patients and those with GT4 infection with an SVR rate exceeding 82% in treatment-naïve patients [34-36]. The addition of the polymerase inhibitor, sofosbuvir (SOF) to pegIFN + RBV enabled triple therapy for patients infected with any HCV GT[37,38].

IFN-free regimens

GT-specific options: Although triple-drug therapies have resulted in higher SVR rates compared to pegIFN + RBV treatment, there is still a major limitation related to side effects as well as contraindications to therapy when using IFN. Patients with liver cirrhosis and hematologic disorders as well as those with decompensated liver disease or severe diseases of other organs and systems were left out of treatment. These safety issues were overcome by the introduction of IFN-free therapies. These well-tolerated and highly effective regimens revolutionized the antiviral therapy of CHC[39]. The first registered DAA that could be used without IFN was SOF[37]. The combination of this drug with the inhibitor of HCV NS5A protein, ledipasvir (LDV), administered with or without RBV resulted in a GT-specific combination active against GT1 and 4 infections.

Randomized, open-label phase 3 trials, ION-1 and ION-2, documented 95%-100% efficacy in GT1-infected patients depending on treatment duration (12 or 24 wk), prior treatment history and RBV use. However, lower efficacy was observed in treatment-experienced patients with liver cirrhosis[40,41] (Table 1). The ION-3 study demonstrated that in treatment-naïve patients without liver cirrhosis even shortening SOF/LDV ± RBV therapy to 8 wk does not significantly affect efficacy[42].

The results of a retrospective real-world evidence (RWE) study conducted in a large cohort of patients in the United States confirmed the high effectiveness of this regimen with 93% of GT1-infected patients responding in 93% ($n = 9912$), while the cure rate in GT4-infected patients was 87% ($n = 97$)[43].

Another GT-specific option registered for patients with compensated liver disease was the combination of ombitasvir (OBV), an inhibitor of NS5A, and ritonavir-boosted paritaprevir (PTV/r), an HCV protease inhibitor. In cases of infection with GT4, it was used with RBV for 12 wk, while for GT1-infected patients the addition of a third DAA, dasabuvir (DSV), acting as a polymerase inhibitor, was obligatory[44]. The addition of RBV and the length of therapy depended on the subtype and the presence of liver cirrhosis.

The phase 3 clinical trials SAPPHERE-I and SAPPHERE-II confirmed the efficacy of the 12-wk option of OBV/PTV/r + DSV + RBV at the level of 96% in GT1-infected patients without liver cirrhosis regardless of history of previous therapy [45,46]. Results from the phase 3 PEARL-III and PEARL-IV clinical trials proved that the inclusion of RBV improved efficacy in GT1a-infected patients, while the SVR in GT1b-infected patients exceeds 99% regardless of RBV addition[47].

The findings of the phase 3b study GARNET allowing the shortening of OBV/PTV/r + DSV therapy in GT1b-infected patients without cirrhosis to 8 wk without affecting efficacy formed the basis for updating the label[48]. Patients with GT4 infection both with and without compensated cirrhosis treated with OBV/PTV/r + RBV in the multinational AGATE-I and AGATE-I part II trials and the Egyptian AGATE-II trial achieved high SVR rates of 96%-100%. The demonstration that prolonging therapy did not improve the success rate among patients with compensated cirrhosis became the basis for updating the label, and regardless of the severity of liver disease, GT4-infected patients received a 12-wk treatment course [49-51]. The high effectiveness of the OBV/PTV/r + DSV +/- RBV regimen of 95% to 100% in GT1 and GT4-infected patients regardless of the severity of liver disease[52-54] and history of prior antiviral treatment has been confirmed in numerous real-world studies[55-57].

Another GT-specific DAA regimen designed for patients with GT1 and GT4 infection without cirrhosis and with compensated cirrhosis includes combinations of the protease inhibitor, grazoprevir (GZR), and the NS5A inhibitor, elbasvir (EBR), used for 12 wk. The option to add RBV and extend therapy to 16 wk applies to GT1a and GT4-infected patients with an initial viral load > 800000 IU/mL. Efficacy in phase 3 clinical trials in treatment-naïve patients without cirrhosis and those with compensated cirrhosis was 97% and 94%, respectively, while treatment-experienced patients responded in 96.6% and 93.8%, respectively[58,59]. However, it should be emphasized that these are data calculated for

Table 1 Efficacy of genotype-specific regimens in phase III of clinical trials

Ref.	Number of participants	Regimen	GT	SVR (mITT analysis) n/N (%)			
				Patients without cirrhosis		Patients with cirrhosis	
				Treatment-naïve	Treatment-experienced	Treatment-naïve	Treatment-experienced
Afdhal <i>et al</i> [40] (ION-1)	865	LDV/SOF, 12 wk (<i>n</i> = 214)	1	179/179 (100)		32/33 (97.0)	
		LDV/SOF + RBV, 12 wk (<i>n</i> = 217)		178/178 (100)		33/33 (100)	
		LDV/SOF, 24 wk, (<i>n</i> = 217)		181/182 (99.5)		31/32 (96.9)	
		LDV/SOF + RBV, 24 wk (<i>n</i> = 217)		179/179 (100)		36/36 (100)	
Afdhal <i>et al</i> [41] (ION-2)	440	LDV/SOF, 12 wk (<i>n</i> = 109)	1		83/87 (95.4)		19/22 (86.4)
		LDV/SOF + RBV, 12 wk (<i>n</i> = 111)			89/89 (100)		18/22 (81.8)
		LDV/SOF, 24 wk, (<i>n</i> = 109)			86/87 (98.9)		22/22 (100)
		LDV/SOF + RBV, 24 wk (<i>n</i> = 111)			88/89 (98.9)		22/22 (100)
Kowdley <i>et al</i> [42] (ION-3)	647	LDV/SOF, 8 wk (<i>n</i> = 215)	1	202/214 (94.4)			
		LDV/SOF + RBV, 8 wk (<i>n</i> = 216)		201/211 (95.3)			
		LDV/SOF, 12 wk (<i>n</i> = 216)		206/209 (98.6)			
Feld <i>et al</i> [45] (SAPPHIRE-I)	473	OBV/PTV/r + DSV + RBV, 12 wk	1	455/473 (96.2)			
Zeuzem <i>et al</i> [46] (SAPPHIRE-II)	297	OBV/PTV/r + DSV + RBV, 12 wk	1		286/297 (96.3)		
Ferenci <i>et al</i> [47] (PEARL-III)	419	OBV/PTV/r + DSV + RBV, 12 wk (<i>n</i> = 210)	1b	209/210 (99.5)			
		OBV/PTV/r + DSV + placebo, 12 wk (<i>n</i> = 209)		207/207 (100)			
Ferenci <i>et al</i> [47] (PEARL-IV)	305	OBV/PTV/r + DSV + RBV, 12 wk (<i>n</i> = 100)	1a	97/99 (98.0)			
		OBV/PTV/r + DSV + placebo, 12 wk (<i>n</i> = 205)		185/204 (90.7)			
Welzel <i>et al</i> [48] (GARNET)	163	OBV/PTV/r + DSV, 8 wk	1b	160/162 (99.0)			
Asselah <i>et al</i> [49] (AGATE-I)	120	OBV/PTV/r + RBV, 12 wk (<i>n</i> = 59)	4			57/58 (98.0)	
		OBV/PTV/r + RBV, 16 wk (<i>n</i> = 61)				60/60 (100)	
Asselah <i>et al</i> [50] (AGATE-I Part II)	64	OBV/PTV/r + RBV, 24 wk	4			60/60 (100)	
Waked <i>et al</i> [51] (AGATE-II)	160	OBV/PTV/r + RBV, 12 wk (<i>n</i> = 131)	4	94/98 (96.0)	30/31 (97.0)		
		OBV/PTV/r + RBV, 24 wk (<i>n</i> = 29)				27/28 (96.0)	
Zeuzem <i>et al</i> [58] (C-EDGE treatment naïve)	421	GZR/EBR ± RBV, 12 wk	1, 4, 6	68/70 (97.0) ¹		231/246 (94.0) ¹	
Kwo <i>et al</i> [59] (C-EDGE treatment-experienced)	420	GZR/EBR ± RBV, 12 or 16 wk	1, 4, 6		255/264 (96.6)		135/144 (93.8)

¹Intent-to-treat analysis (no data for modified intent-to-treat analysis).

DSV: Dasabuvir; EBR: Elbasvir; GT: Genotype; GZR: Grazoprevir; LDV: Ledipasvir; mITT: Modified intention-to-treat; OBV: Ombitasvir; PTV/r: Paritaprevir; RBV: Ribavirin; SOF: Sofosbuvir; SVR: Sustained virological response.

intent-to-treat analysis.

Pangenotypic options: The first available DAA regimen with activity against all HCV GTs was a combination of SOF and RBV. The efficacy of 12 wk of therapy with SOF + RBV in treatment-naïve patients with GT1-3 infection evaluated in a phase 3 clinical trial was 72% in patients without cirrhosis and 47% in patients with cirrhosis, respectively[60] (Table 2). A higher response rate of 97.1% was documented in patients with GT2 infection. The efficacy of this regimen in treatment-experienced GT2 and GT3-infected patients participating in the phase 3 FUSION study was 96% *vs* 37% for patients without cirrhosis and 60% *vs* 19% in patients with cirrhosis, respectively[61]. Extending the duration of therapy to 16 wk increased the cure rates to 100% and 62.5% in patients without cirrhosis infected with GT2 *vs* GT3, while patients with liver cirrhosis responded in 62.5% and 61.0%, respectively. A comparison of treatment duration (16 wk *vs* 24 wk) in patients with GT3 infection documented the higher efficacy followed longer therapy with SVR of 86.5% and 78.6% in patients without cirrhosis and those with cirrhosis, respectively[62].

Extending treatment to 24 wk improved the response rate, especially in the GT3-infected treatment-experienced patients with cirrhosis responding in 76%. These values were still unsatisfactory, and the regimen was considered suboptimal in this patient population[62,63,64].

The use of a 12-wk regimen with pangenotypic activity, consisting of SOF and DCV, improved SVR rates in GT3-infected patients without cirrhosis to about 97% in treatment-naïve individuals and 94% in those who failed prior therapy. However, the efficacy reported in patients with cirrhosis was much lower, approximately 63%[65].

A real breakthrough in the treatment of CHC came with the introduction of new pangenotypic options highly effective against all HCV GTs. Based on phase 3 ASTRAL registration studies, in 2016 the Food and Drug Administration approved a combination consisting of SOF and the NS5A inhibitor velpatasvir (VEL) for patients without and with liver cirrhosis, including decompensated individuals[66]. The 12-wk regimen in patients with compensated liver disease resulted in an SVR of 95%-100% regardless of the history of previous therapy, while patients with decompensated liver cirrhosis responded in 84%[67-69]. The extension of therapy to 24 wk in this patient population increased the response rate to 88% and the addition of RBV to 94% in the modified intent-to-treat analysis[69]. The lowest efficacy was achieved in GT3-infected patients, with SVR rates ranging from 50% to 85%, but it should be noted that the number of patients in this study was relatively small, 12-14 in each treatment arm.

The high efficacy of SOF/VEL was confirmed in a meta-analysis of 12 studies from routine clinical practice. Of the 5196 patients with response rate data, 99% achieved SVR[70]. The analysis revealed unfavorable factors associated with a reduction in the odds of virologic response to about 98%, such as GT3 and compensated liver cirrhosis. Importantly, patients with current or prior decompensated cirrhosis were excluded from the analysis. Another new pangenotypic option containing the protease inhibitor glecaprevir (GLE) and the NS5A inhibitor pibrentasvir (PIB) became available for patients with compensated liver disease after approval by Food and Drug Administration in 2017[71].

The efficacy of the 12-wk GLE/PIB regimen in patients with GT 1, 2, 4-6 infection without cirrhosis as well as with compensated cirrhosis participating in phase 3 clinical trials reached 100% and 99%, respectively[72-74]. An equally high efficacy of 99% was reported in GT3-infected patients without liver cirrhosis in the phase 3 ENDURANCE-3 trial[72].

Shortening therapy to 8 wk in patients infected with GT1-6 without cirrhosis evaluated in the SURVEYOR-I and -II phase 2 studies and with compensated cirrhosis participating in the EXPEDITION-8 phase 3 trial did not affect the efficacy of therapy and became the basis for updating the label[75,76]. However, the EudraCT trial showed that further reduction of therapy to 4 wk reduced efficacy to 59% (10/17) for GLE/PIB without RBV and to 73% (11/15) for GLE/PIB + RBV, and drug target-specific substitutions associated with NS5A resistance were identified as a predictor of virologic failure[77].

The registration of the GLE/PIB option for use in GT1-6-infected patients with stage 4 or 5 chronic kidney disease, including those on dialysis, was based on the results of the EXPEDITION-4 trial with a 98% SVR rate in this population of patients[78]. The high efficacy of treatment with the GLE/PIB regimen has been confirmed in everyday clinical practice. A meta-analysis of 18 RWE studies involving 12531 patients documented greater than 95% efficacy regardless of GT, presence of compensated cirrhosis and history of prior therapy[79].

In 2017, a new triple pangenotypic regimen containing SOF/VEL and the HCV protease inhibitor voxilaprevir (VOX) was also registered for patients with compensated liver disease[80]. Despite its high efficacy regardless of the history of previous therapy, in practice it is used primarily as a rescue regimen after the failure of DAA therapy, and it is discussed in detail later in this manuscript, in the section on rescue therapy.

CHANGES IN THE PROFILE OF HCV-INFECTED PATIENTS OVER TIME

The availability of safe and effective therapy has led the WHO to set a goal of eliminating HCV as a significant public threat by 2030. This goal was defined as a 65% reduction in mortality and a 90% reduction in new chronic infections compared to 2015[85]. In June 2021, the WHO presented targets to reduce the annual incidence to ≤ 5 per 100000 and annual mortality to ≤ 2 per 100000[86]. In a large model study representing 93% of the global population, the Polaris Observatory HCV Collaborators estimated a reduction in global HCV prevalence from 0.9% (63.6 million) in 2015 to 0.7%

Table 2 Efficacy of pangenotypic regimens in phase III of clinical trials

Ref.	Number of participants	Regimen	GT	SVR (mITT analysis) n/N (%)			
				Patients without cirrhosis		Patients with cirrhosis	
				Treatment-naïve	Treatment-experienced	Treatment-naïve	Treatment-experienced
Lawitz <i>et al</i> [60] (FISSION)	256	SOF + RBV, 12 wk	1-3	147/204 (72.1)		23/49 (46.9)	
Jacobson <i>et al</i> [61] (FUSION)	201	SOF + RBV, 12 wk (<i>n</i> = 103)	2, 3		25/26 (96.2), 14/38 (36.8)		6/10 (60.0), 5/26 (19.2)
		SOF + RBV, 16 wk (<i>n</i> = 98)	2, 3		23/23 (100), 25/40 (62.5)		7/9 (77.8), 14/23 (60.9)
Jacobson <i>et al</i> [61] (POSITION)	207	SOF + RBV, 12 wk	2		85/92 (92.0%)		16/17 (94.0%)
			3		57/84 (68.0%)		3/14 (21.0%)
Zeuzem <i>et al</i> [81] (VALENCE) ¹	323	SOF + RBV, 12 wk (<i>n</i> = 73)	2	29/30 (96.7)	30/32 (93.8)	2/2 (100)	7/9 (77.8)
		SOF + RBV, 24 wk (<i>n</i> = 250)	3	87/92 (94.6)	85/98 (86.7)	12/13 (92.3)	29/47 (61.7)
Omata <i>et al</i> [82]	153	SOF + RBV, 12 wk	2	80/82 (95.0)	52/54 (100)	8/8 (100)	8/9 (89.0)
Foster <i>et al</i> [62] (BOSON) ¹	363	SOF + RBV, 16 wk	3	58/70 (83.0)	41/54 (76.0)	12/21 (57.0)	17/36 (47.0)
		SOF + RBV, 24 wk		65/72 (90.0)	44/54 (81.0)	18/22 (82.0)	26/34 (76.0)
Satsangi <i>et al</i> [83]	105	SOF + RBV, 24 wk	3	49/49 (100)	1/1 (100)	22/23 (95.6)	3/3 (100)
Nelson <i>et al</i> [65] (ALLY-3)	152	DCV + SOF, 12 wk	3	105/109 (96.0)		20/32 (63.0)	
				73/75 (97.0)	32/34 (94.0)	11/19 (58.0)	9/13 (69.0)
Feld <i>et al</i> [67] (ASTRAL-1)	624	SOF/VEL, 12 wk	1, 2, 4, 5, 6	496/501 (99.0)		120/121 (99.2)	
Foster <i>et al</i> [68] (ASTRAL-2)	266	SOF/VEL, 12 wk (<i>n</i> = 134)	2	133/134 (99.0)			
		SOF + RBV, 12 wk (<i>n</i> = 132)		124/132 (94.0)			
Foster <i>et al</i> [68] (ASTRAL-3)	552	SOF/VEL, 12 wk (<i>n</i> = 277)	3	160/163 (98.0)	31/34 (91.0)	40/43 (93.0)	33/37 (89.0)
		SOF + RBV, 24 wk (<i>n</i> = 275)		141/156 (90.0)	22/31 (71.0)	33/45 (73.0)	22/38 (58.0)
Curry <i>et al</i> [69] (ASTRAL-4)	267	SOF/VEL, 12 wk (<i>n</i> = 90)	1-6			75/89 (84.3)	
		SOF/VEL + RBV 12 wk (<i>n</i> = 87)				82/87 (94.0)	
		SOF/VEL, 24 wk (<i>n</i> = 90)				77/87 (88.5)	
Forns <i>et al</i> [73] (EXPEDITION-1)	146	GLE/PIB, 12 wk	1, 2, 4, 5 or 6			145/146 (99.0)	
Zeuzem <i>et al</i> [81] (ENDURANCE-1)	703	GLE/PIB, 8 wk (<i>n</i> = 351)	1	343/344 (99.7)			
		GLE/PIB, 12 wk (<i>n</i> = 352)		345/345 (100)			
Zeuzem <i>et al</i> [72] (ENDURANCE-3)	505	GLE/PIB, 12 wk (<i>n</i> = 233)	3	214/217 (99.0)			
		SOF + DCV, 12 wk (<i>n</i> = 115)		110/111 (99.0)			
		GLE/PIB, 8 wk (<i>n</i> = 157)		143/149 (96.0)			
Asselah <i>et al</i> [74]	202	GLE/PIB, 12 wk	2	192/192 (100)			

(ENDURANCE-2)					
Asselah <i>et al</i> [74] (ENDURANCE-4)	121	GLE/PIB, 12 wk	4-6	120/120 (100)	
Brown <i>et al</i> [76] (EXPEDITION-8)	343	GLE/PIB, 8 wk	1-6		334/335 (99.7)
Gane <i>et al</i> [78] (EXPEDITION-4)	104	GLE/PIB, 12 wk	1-6	102/104 (98.0)	
Bourlière <i>et al</i> [84] (POLARIS-1) ¹	263	SOF/VEL/VOX, 12 wk	1-6	253/263 (96.0) ²	
Bourlière <i>et al</i> [84] (POLARIS-4) ¹	182	SOF/VEL/VOX, 12 wk	1-4	178/182 (98.0) ²	

¹Intent-to-treat analysis (no data for modified intent-to-treat analysis).

²All analyzed patients were previously treated with a direct-acting antiviral-containing regimen.

DCV: Daclatasvir; GLE: Glecaprevir; GT: Genotype; mITT: Modified intention-to-treat; PIB: Pibrentasvir; RBV: Ribavirin; SOF: Sofosbuvir; SVR: Sustained virological response; VEL: Velpatasvir; VOX: Voxilaprevir.

(56.8 million) in 2020. During the analysis period, 8.7 million patients worldwide were treated, and significant changes were observed in the demographic and clinical characteristics of HCV-infected patients[87].

Published data indicated that patients treated with antiviral therapy for chronic HCV infection were less burdened by comorbidities and were less likely to use comedications in the subsequent time intervals analyzed[88-91]. A decrease in the median age of treated patients was also observed. Elsharkawy *et al*[88] analyzed the data of 337042 Egyptian patients of the national CHC treatment program who started therapy from October 2014 (the first introduction of IFN-free regimens in Egypt) to March 2016. The population was divided into three-time intervals of 6 mo each. The results showed a reduction in age (mean $\pm$ SD) from 53 ± 9 years in the first cohort to 49 ± 12 years in the last group[88,92]. In the Polish cohort of 10152 patients observed between 2015 and 2018, a more pronounced reduction in median age was observed from 58 at the beginning of the analyzed period to 49 at the end[89]. Furthermore, the prevalence of comorbidities and the use of concomitant medications decreased significantly in subsequent time intervals from 68.6% to 59.5% and from 64.6% to 57.7%, respectively[89].

A study carried out in the United States documented a 9.3% increase in the proportion of HCV RNA-positive patients under the age of 50 between 2017 and 2019, while German observations covering the period 2014-2018 demonstrated an increase of 14.7% in this age group of treated patients[90,91].

In 2015, Messina *et al*[3] published a comprehensive study on the prevalence and distribution of GTs worldwide before the IFN-free era. The analysis included 1217 studies published between 1993 and 2013, and they documented GT1 as the most common HCV GT globally (46%), followed by GT3 and GT4 (30% and 9%, respectively). The prevalence of GTs showed geographic variation; the proportion of GT4 in central sub-Saharan Africa accounted for more than 97% of all HCV infections. At the end of 2015, the estimated order of GTs remained the same, with GT1 and GT3 being the dominant GTs worldwide at 44% and 25% prevalence, respectively, and GT4 continuing to rank third with a 15% prevalence[93]. Given the high efficacy of pangenotypic regimens, the need for genotyping seems to be losing ground [94], and to the best of our knowledge, no studies have been published in the last few years on the prevalence and distribution of GTs at the global level.

However, several papers have analyzed this issue in patient populations at the national level. Studies of Polish and German cohorts have shown a high proportion of GT1-infected patients among antiviral-treated patients at the beginning of the DAA era[89,95]. Over time, the proportion of these patients has declined in favor of GT3-infected patients. The explanation for this phenomenon is related to the changes in therapeutic regimens discussed above. At the beginning of the DAA era, GT1-infected patients had access to highly effective GT-specific regimens, while for patients with GT3 infection there was only one IFN-free option, the 24-wk SOF + RBV combination. Because of the suboptimal virologic response achieved with this regimen, many GT3-infected patients, especially those with non-advanced liver disease, preferred the shorter 12-wk triple-drug treatment of SOF + pegIFN + RBV or waiting for more effective IFN-free options [63]. Another IFN-free therapeutic option that was more effective in patients with GT3 infection, the SOF + DCV + RBV combination, was not widely available in many countries since it contained drugs from different manufacturers, and this made registration and reimbursement difficult.

Thus the prevalence of GT1-infected DAA-treated patients decreased by 9% in Poland between 2015 and 2018 and 12% in Germany between 2014 and 2019. A similar trend was observed among 76110 patients after the introduction of DAA regimens in China, with the percentage of GT3-infected patients increasing by almost 6% between 2016 and 2020[96].

At the beginning of the IFN-free era, the proportion of patients with advanced fibrosis and cirrhosis was significantly higher compared to subsequent years, likely related to priority access to reimbursable DAA options in this patient population[97]. A single-center RWE study of Polish patients documented that the percentage of patients on antiviral therapy who were diagnosed with cirrhosis decreased significantly from 51% in 2015-2016 to 11.8% in 2018[98].

SPECIFIC SUBPOPULATIONS OF HCV-INFECTED PATIENTS

In the era of IFN-based antiviral therapies, specific subpopulations of patients were identified and recognized as difficult to treat because of more prevalent contraindications to therapy, poorer adherence, more frequent adverse events with associated treatment discontinuation and lower efficacy[4,25]. In the era of DAA therapy, these populations are essentially no longer difficult to treat, although some researchers have noted factors that negatively affect the success of therapy, especially if they occur together.

Patients with HCV/HIV coinfection

The prevalence of HCV/HIV coinfection varies significantly across subpopulations and geographic regions. Recent estimates have shown that about 2.5% of HIV-infected patients are coinfecting with HCV[99]. In the era of IFN-based regimens, HIV/HCV coinfecting patients were considered more challenging compared to those with HCV mono-infection. Inferior adherence, lower SVR rates, drug interactions and unfavorable safety profiles were significant therapeutic concerns[100]. DAA therapy has revolutionized the treatment of HIV/HCV-coinfecting individuals, improving adherence, efficacy and safety profile. Clinical trials using a range of DAA options have shown high rates of SVR exceeding 95% and comparable to efficacy in patients with HCV mono-infection regardless of the type of regimen used[101-104]. Similar high effectiveness has been observed in studies carried out in routine medical practice, although some authors have reported lower response rates to DAA therapy in populations with HIV coinfection than in populations with HCV mono-infection [105-109].

Treatment-experienced patients

Similar observations apply to patients with a history of prior failed therapy. Numerous clinical trials with different DAA options do not document the lower SVR rates as compared to treatment-naïve patients, while in some RWE studies this parameter has been identified as an unfavorable factor in the chances of virologic response with lower SVR rates ranging from 0.7% to 2.4% depending on the regimen used, type of GT and severity of liver disease[39,55,70,73,110].

A distinct category of treatment-experienced patients is those who have not responded to IFN-free options subjected to subsequent DAA therapy. Data from the German hepatitis C registry described an unsatisfactory 79.5% response rate in patients retreated with DAA after the failure of initial IFN-free treatment[111]. These results were supported by findings from a Polish RWE study reporting effectiveness of 86% with GT-specific DAA retreatment in previous IFN-free nonresponders[112]. A newly published analysis also from Poland evaluated patients who failed pangenotypic therapy and underwent pangenotypic retreatment[113].

Patients with renal impairment

Chronic infection with HCV may be an independent risk factor for the development or progression of chronic kidney disease (CKD)[114]. On the other hand, due to suboptimal hygiene measures in some dialysis units, the prevalence of HCV infection in hemodialysis patients was significantly higher (3.8%-31.1%)[115]. Historically, the use of IFN + RBV therapy in patients with renal failure has been limited due to contraindications to both medications[116]. Also, the efficacy of the IFN-based regimen in this patient population was lower and the safety profile was inferior compared to patients with normal renal function. Hemodialyzed patients with CHC treated with pegIFN analyzed in a meta-analysis of 24 clinical trials achieved an SVR rate of 40%, while 14% of them discontinued treatment due to adverse events[117]. Due to the distinct metabolic pathways of DAAs, their introduction to treatment has offered an effective and well-tolerated therapy for patients with renal impairment, including hemodialysis patients with HCV infection[118].

SOF-containing regimens are approved for use in patients with estimated glomerular filtration rate > 30 mL/min/1.73 m² due to limited safety data in patients with severe renal impairment. However, since 2019 according to the label, these combinations can also be administered with no dose adjustment at lower estimated glomerular filtration rate values and in patients requiring hemodialysis if no other relevant treatment options are available[94,119,120]. The meta-analysis included 21 studies with 717 patients in CKD stages 4-5, demonstrating an SVR of 97% and a good safety profile of SOF-containing regimens[121]. Therapy should be used with caution, and renal parameters should be carefully monitored during the treatment course due to the possibility of worsening renal function, as demonstrated by Saxena *et al*[122].

Among GT-specific options, the OBV/PTV/r +/- DSV and GZR/EBR regimens are registered for use in patients with renal failure, including those on dialysis[44,123]. The RUBY-1 and RUBY-2 clinical trials demonstrated an SVR of 95% in HCV-infected patients in CKD stage 4-5 treated with OBV/PTV/r +/- DSV +/- RBV, while the therapy with GZR/EBR in this patient population evaluated in C-SURFER study resulted in 99% efficacy[124,125]. Of the pangenotypic options, the GLE/PIB regimen has been registered for patients with severe renal failure, including those on dialysis; the good safety profile and high efficacy of this combination were documented in clinical trials[78,126].

Patients with compensated liver cirrhosis

The efficacy achieved in compensated liver patients with cirrhosis treated with GT-specific options ranged from 92% to 96%, while clinical trials evaluating pangenotypic regimens in this patient population showed an SVR of 96% and above [67,76,127,128]. Although these results corresponded with high treatment efficacy, they were lower compared to SVR in patients without cirrhosis[67,76,129]. Data from the RWE study confirmed the worse effects of therapy in the population with cirrhosis than in patients without cirrhosis. Moreover, decompensation of liver function was identified as an independent negative predictor of SVR[69,110,130]. It should be noted that IFN-based therapies were absolutely contraindicated in patients with decompensated cirrhosis due to the side effects of this cytokine[131]. Also, not all DAA regimens are registered for use in this patient population. Combinations containing protease inhibitors are not recommended

because of the risk of worsening liver function[94]. Among GT-specific regimens, the SOF/LDV option is approved for use in patients with decompensated cirrhosis. Among pangenotypic regimens, it applies to SOF ± DCV ± RBV and SOF/VEL combinations[132-134].

Other factors affecting treatment outcome

Male sex is recognized as a factor that may reduce the effectiveness of DAA therapy. Multivariate logistic regression models performed in a large retrospective analysis of 17487 United States veterans with HCV infection found that the male sex was an independent negative predictor of achieving SVR[43]. These data confirm the results of other RWE analyses conducted in numerically smaller populations[110,135].

Patients with GT3 infection, who were considered an easy-to-treat population in the era of IFN-based therapy, are less likely to respond to treatment in the era of DAAs[43,136,137].

RESCUE REGIMENS

Despite the very high efficacy of currently available DAA therapy exceeding 95%, there is still a small proportion of patients who do not respond to treatment, especially when different negative predictors of achieving SVR are present [113,138]. Failure of therapy with DAA regimens could be related to the selection of mutant-resistant strains carrying resistance-associated substitutions, and those contributing lower sensitivity to NS5A inhibitors are the most persistent [139]. The only therapeutic option registered for treatment in such cases is a three-drug pangenotypic combination of SOF/VEL/VOX. The introduction of this regimen improved the SVR rates to 96%-98% in patients after the failure of DAA therapy evaluated in POLARIS-1 and POLARIS-4 clinical trials[84,80]. The findings from registration studies are supported by data from routine medical practice[113,140,141]. A meta-analysis of 10 cohorts including 1187 patients demonstrated that 96% of them achieved undetectable HCV RNA 12 wk after the end of treatment. However, lower effectiveness was reported for those with GT3 infection and cirrhosis[140,141].

According to the most recent European Association for the Study of the Liver and American Association for the Study of Liver Diseases guidelines, in patients who have failed SOF/VEL/VOX, extended retherapy with this regimen plus weight-based RBV or a combination of GLE/PIB + SOF + RBV is recommended, although no data from clinical trials for SOF/VEL/VOX nonresponders are available[94,142]. It was pointed out that retreatment can be optimized based on resistance-associated substitution testing[94]. A 96% efficacy of the rescue regimen of GLE/PIB in combination with SOF and RBV was evaluated in the MAGELLAN-3 clinical trial, but all 23 included participants were GLE/PIB failures[143].

Very limited data on patients receiving GLE/PIB + SOF +/- RBV retherapy are available from RWE studies. In an open-label study conducted in New Zealand, patients treated with GLE/PIB + SOF after prior DAA failure achieved a virologic rate of 98%[144].

CONCLUSION

Since the beginning of the availability of IFN-free options, we have observed changes occurring in the regimens used from GT-specific to highly potent pangenotypic options, including rescue combinations. These are accompanied by changes in the profile of the HCV-infected population, with patients starting treatment over time being younger, with less advanced liver disease and less burdened by comorbidities. Despite the very high effectiveness of current DAA options, some factors including male sex, GT3 infection, liver cirrhosis and prior failure of DAA therapy are still identified that lower the chances of a cure.

FOOTNOTES

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Country/Territory of origin: Poland

ORCID number: Michał Brzdęk 0000-0002-1180-9230; Dorota Zarębska-Michałuk 0000-0003-0938-1084; Robert Flisiak 0000-0003-3394-1635.

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