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Original research article

Effectiveness and safety of ledipasvir/sofosbuvir ± ribavirin in the treatment of HCV infection: The real-world HARVEST study

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ABSTRACT

Background: To evaluate the effectiveness and safety of ledipasvir/sofosbuvir (LDV/SOF) ± ribavirin (RBV) regimen in a real-world setting.
Methods: Patients received a fixed-dose combination tablet containing LDV and SOF with or without RBV, for 8, 12 or 24 weeks. Patients were assessed at baseline, end of treatment, and 12 weeks after the end of treatment. The primary effectiveness endpoint was sustained virologic response 12 weeks after the end of treatment (SVR12).
Results: Of the 86 patients, aged 20–80 years, 82.6% were HCV genotype 1b-infected and 50.0% were cirrhotic. More than half (52.3%) had previously followed pegylated interferon-containing (PEG-IFN) treatment regimens, and 38.5% were null-responders. SVR12 was achieved by 94.2% of patients. All non-responders were cirrhotic: two demonstrated virologic breakthrough and the remaining three relapsed. All patients treated with an 8-week regimen achieved SVR12 despite having high viral load at baseline (HCV RNA of >1 million IU/mL in 8/10 patients, including one with a viral load of >6 million IU/mL).

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Adverse events were generally mild and transient. Most frequently, fatigue (22.1%), headache (15.1%), and arthralgia (7.0%) were observed. Laboratory abnormalities included anemia and hyperbilirubinemia.
Conclusions: Treatment with LDV/SOF ± RBV is an effective and safe option for patients with HCV, including those with advanced liver disease or a history of non-response to PEG-IFN-based therapy.

1. Introduction

The World Health Organization estimates that hepatitis C virus (HCV) currently affects about 130–170 million people worldwide [1]. The majority of infected individuals develop a chronic form of the disease, associated with potentially life-threatening sequelae [2]. Each year, ~700,000 deaths are attributed to HCV, most resulting from liver cirrhosis and cancer [1,3].

For HCV-infected patients, effective therapy can reduce the risk of complications arising from the infection. Until recently, treatment of HCV infection was based primarily on regimens containing pegylated interferon (PEG-IFN), and provided virologic cure in only 41–73% of patients. The success of this regimen has been demonstrated to be dependent on patient genotype, cirrhosis status, and previous treatment history [4]. In addition to poor virologic outcome, on-treatment adverse events (AEs) were common and often life-threatening. Only recently have novel oral anti-HCV therapies been developed and are characterized by good efficacy and safety, as shown in a number of pre-registration studies [5,6].

A combination of ledipasvir/sofosbuvir (LDV/SOF) was registered in the European Union in 2014, and is now recommended for the treatment of chronic HCV infection as a part of current clinical practice [7–10]. A single tablet fixed-dose LDV/SOF with or without ribavirin (RBV) demonstrated good efficacy and safety profile in the clinical trial setting. Phase 3 trials conducted in previously untreated patients with chronic HCV genotype 1 infection, who received LDV/SOF ± RBV for 8, 12 or 24 weeks, revealed sustained virologic response (SVR12) rates of 93–99% [11,12]. Similar results were observed in treatment-experienced patients who received LDV/SOF for 12 or 24 weeks [13]. LDV/SOF alone or in combination with RBV is also registered in the European Union for the treatment of patients with HCV genotype 3, 4, 5 and 6 infection, HCV/HIV co-infection, liver transplant recipients, and decompensated cirrhotics [7]. Data from all pre-registration studies demonstrate that LDV/SOF is generally safe and well-tolerated [11–13].

The nature of randomized controlled trials, which are conducted in selected patient populations in the absence of confounding factors, leads to the limited generalizability of their results to real-life conditions [14,15]. Evidence in support of excellent outcomes of LDV/SOF ± RBV in patients with chronic HCV infection in the real-world setting is growing [16–18], but more research is needed to assess the effectiveness and safety of this regimen in routine clinical practice in particular regions of the world. As such, we designed an investigator-initiated multicenter study, which is the first in central and eastern Europe aimed at evaluating effectiveness and safety of LDV/SOF ± RBV in a diverse population of HCV-infected individuals treated in the setting of a normal medical practice.

2. Materials and Methods

HARVEST was a single-arm observational study conducted in 23 hepatologic centers in Poland. The study drug was donated by Gilead Poland to ensure early access to patients with advanced hepatitis C and contraindications to interferon-based regimens. The study was conducted with respect to Good Clinical Practice guidelines and the Declaration of Helsinki principles for ethical research. Written informed consent was obtained from each patient included in the study.

2.1. Study population

Patients were eligible for inclusion in the study if they were adults aged ≥18 years (male or female), with a chronic HCV infection. Patient treatment history (previously treated or treatment naïve) was not a criterion for inclusion/exclusion. All eligible patients were treated with LDV/SOF ± RBV in accordance with therapeutic guidelines and the manufacturer's recommendations [8,9].

Patients were assessed at day 0, end of treatment (EOT), and 12 weeks after the end of treatment (FU). Additional visits were conducted at day 1, day 7, week 4, and week 8, at the discretion of the treating physician. Baseline evaluation was conducted during the initial study visit, and included gender, age, body weight, fibrosis status according to METAVIR, MELD (Model for End-Stage Liver Disease) and Child-Pugh scores, prior treatment history, comorbidities, and laboratory data (HCV RNA level, liver function tests, platelets count, hemoglobin concentration, alpha fetoprotein, and serum creatinine). The degree of liver fibrosis was determined based on available reports from liver biopsy or non-invasive tests (transient or shear-wave elastography). HCV RNA detection threshold differed across study centers but did not exceed 18 IU/mL. HCV RNA levels were obtained by quantitative PCR assays: COBAS TaqMan HCV v2.0 (Roche), COBAS AmpliPrep HCV (Roche), and m2000 RealTime System (Abbott). The primary effectiveness endpoint was defined as the proportion of patients with undetectable HCV RNA 12 weeks after the end of treatment (SVR12), and the primary safety endpoint were AEs reported from baseline through to 30 days after the final treatment.

2.2. Medication and follow-up

Patients received a single daily dose of LDV/SOF (90/400 mg Harvoni™, Gilead). The initial dose of RBV was generally dependent on body weight (1000 mg/day in patients weighing <75 kg or 1200 mg/day in those weighing ≥75 kg); however, adjustments were made in patients who presented with significant laboratory abnormalities at baseline. In addition, the RBV dose was reduced according to the product characteristics or discontinued in patients who developed severe AEs during observation (anemia, impaired renal function). Treatment duration was 8, 12 or 24 weeks, as determined by the treating physician based on the product characteristics and expert guidelines. The 8-week regimen was reserved to selected treatment-naïve patients with HCV genotype 1b infection and no or moderate fibrosis (METAVIR F0–F2).

2.3. Statistical analysis

Data are presented as mean ± standard deviation (SD). Statistical analysis was carried out using the GraphPad Prism 5.0 (GraphPad Software, Inc, La Jolla, USA) and Microsoft Excel. Samples were analyzed according to the intention-to-treat principle.

3. Results

3.1. Study population

A total of 86 patients (60.5% males) aged 20–80 years were enrolled in the study, 71 genotype 1b-infected 82.6%). Of the patient cohort, 43 (50.0%) were cirrhotic. Forty-five patients (52.3%) had previously received PEG-IFN ± RBV therapy, with 33 (38.4%) being null-responders. Most patients (63/86, 73.3%) received the 12-week regimen. Thirty-seven patients (43.0%) received a daily dose of RBV ranging from 400 to 1200 mg. All 86 patients which started treatment completed follow-up visit to evaluate sustained virologic response. Baseline demographic and clinical characteristics of the study population are summarized in Table 1.

3.2. Effectiveness

SVR12 was achieved by 94.2% (81/86) of patients. Five patients – all male, cirrhotic and genotype 1b-infected – failed the regimen: two had a virologic breakthrough and three suffered post-treatment relapse. Detailed characteristics of this group are presented in Table 2. SVR12 was achieved by 93.4% (71/76) of patients treated for 12 weeks. All (10/10) patients treated for 8 weeks achieved SVR12 despite having a high viral load at baseline (HCV RNA of $>10^6$ IU/mL in 8/10 patients, including one patient with HCV RNA of $>6 \times 10^6$ IU/mL). Clinical and laboratory data of the patients treated for 8 weeks, as well as details on the virologic response of these patients, are summarized in Table 3.

SVR12 rates ranged from 75 to 100%, depending on baseline characteristics and RBV use. Effectiveness outcomes across subgroups are presented in Fig. 1. SVR12 of 100% was observed in female and non-cirrhotic patients. A <90% response rate was seen in patients with cirrhosis, Child-Pugh B or C, decreased platelet count, and hypoalbuminemia. Virologic response during treatment and follow-up is presented in Fig. 2.

Table 1
Baseline demographic and clinical characteristics, n = 86.

	n = 86
Males, %	60.5
Age, years, mean (±SD)	49 (13)
BMI, kg/m^{2,} mean (±SD)	27 (6)
Duration of treatment (weeks), mean (±SD)	
8	10 (11.6)
12	63 (73.3)
24	13 (15.1)
History of liver transplantation, n (%)	4 (4.6)
HCV RNA, IU/mL, mean (±SD)	1.5×10^6 (2.0)
ALT, IU/mL, mean (±SD)	98 (90)
PLT, mean (±SD)	142,000 (94,000)
Albumins, g/dL, mean (±SD)	3.9 (0.8)
Fibrosis, n (%)	
F0	1 (1.2)
F1	10 (11.6)
F2	15 (17.4)
F3	14 (16.3)
F4	43 (50.0)
Unknown	3 (3.5)
Genotype, n (%)	
1a	1 (1.2)
1b	71 (82.6)
1, unknown subgenotype	9 (10.5)
3	1 (1.2)
4	4 (4.7)
Treatment history, n (%)	
Naive, n (%)	38 (44.2)
Previous PEG-IFN-based therapies, n (%):	
Relapse	8 (9.3)
Partial response	1 (1.2)
Null response	33 (38.5)
Discontinuation	3 (3.5)
Unknown	3 (3.5)

Data are presented as mean (SD) unless indicated otherwise. ALT, alanine aminotransferase; BMI, Body Mass Index; HCV RNA, hepatitis C virus ribonucleic acid; PLT, platelet count.

3.3. Safety

The treatment was generally well-tolerated. AEs were experienced by 69/86 patients (80.2%) and were predominantly mild and

Table 2
Characteristics of patients who failed LDV/SOF ± RBV, n = 5.

		Patients who failed the treatment				
		1	2	3	4	5
Gender	male	●	●	●	●	●
	female					
Genotype	1a					
	1b			●	●	●
	1, unknown subtype	●				
	3					
	4		●			
HCV RNA, IU/mL	$<10^6$	●		●	●	
	$\geq 10^6$		●			●
Cirrhosis	yes	●	●	●	●	●
	no					
Treatment-naive	yes	ND		ND		●
	no		●		●	
Albumins, g/dL	<3.5	●		●	●	
	≥3.5		●			●
PLT, cells/μL	<100,000	●		●	●	●
	≥100,000		●			
RBV	yes	●				
	no		●	●	●	●
Child-Pugh	A		●			●
	>A	●		●	●	
Mechanism of virologic failure	relapse	●		●		●
	virologic breakthrough		●		●	

HCV RNA, hepatitis C virus ribonucleic acid; ND, no data; PLT, platelet count.

Table 3
Clinical characteristics and virologic response (HCV RNA, IU/mL) of patients treated for 8 weeks, n = 10.

Clinical characteristics										
	1	2	3	4	5	6	7	8	9	10
Gender	F	F	F	F	M	F	M	M	M	F
Age, years	47	53	20	64	38	50	38	42	58	54
Treatment history	NAI	NAI	NAI	NAI	NAI	NAI	NAI	NAI	NAI	NAI
Elastography, kPa	7.9[a]	6.3[a]	8.1[a]	7.9[a]	4.9[a]	4.1[a]	7.2[a]	6.9[a]	7.3[a]	6.8[b]
Fibrosis	F2	F0/1	F2	F2	F0/1	F0/1	F2	F0/1	F2	F2
Genotype	1b	1b	1b	1b	1b	1b	1b	1b	1b	1b
RBV	0	0	0	0	0	0	0	0	0	0

Virologic response										
	1	2	3	4	5	6	7	8	9	10
d0	1490	209000	1080000	3280000	1880000	5900000	3700000	1880000	10400000	1354775
d1	TND	213	712	12500	1440	3850	2320	1500	18700	ND
d7	TND	TND	44.6	352	65.1	138	30	TD	701	ND
w4	TND	TND	TND	TND	TND	TND	TND	TND	TND	TND
EOT	TND	TND	TND	TND	TND	TND	TND	TND	TND	TND
FU	TND	TND	TND	TND	TND	TND	TND	TND	TND	TND

EOT, end of treatment; F, female; FU, follow-up 12 weeks after EOT; M, male; NAI, treatment naive; RBV, ribavirin; TD, HCV RNA detectable but below the limit of quantification; TND, HCV RNA undetectable; ND, no data.
[a] Aixplorer.
[b] Fibroscan.

manageable. Most frequently, fatigue (22.1%), headache (15.1%), and arthralgia (7.0%) were observed. Hemoglobin levels below 10 g/dL were recorded in 8.1% of patients, more often in the RBV-treated group (16.2% of patients who received SOF/LDV + RBV vs. 2.0% of patients who received SOF/LDV only). RBV treatment was ceased in two patients due to anemia, and in one patient the dose was reduced to 400 mg/day. Three patients (3.5%), all of whom had received RBV as part of their antiviral therapy, developed hyperbilirubinemia. The treatment was ceased prematurely in two patients. One of them developed AE (diarrhea) that required treatment cessation, in another patient therapeutic failure was observed. A summary of clinical and laboratory AEs is presented in Table 4.

4. Discussion

This prospective, non-interventional study confirms good safety, effectiveness and tolerability of LDV/SOF ± RBV in the treatment of HCV infection in clinical practice. The proportion of patients with SVR12 was 94.2%, with rates ranging from 75% to 100% across subgroups. The proportion of responders was similar to that observed in the previously published ION-1, ION-2 and ION-3 randomized controlled trials [11–13]. In these trials, SVR12 ranged from 93–99% in treatment-naïve and from 94–99% in treatment-experienced patients, with best results observed in the 24-week regimen [19]. In our study, comparable antiviral effectiveness was achieved in both 8- and 12-week groups. We

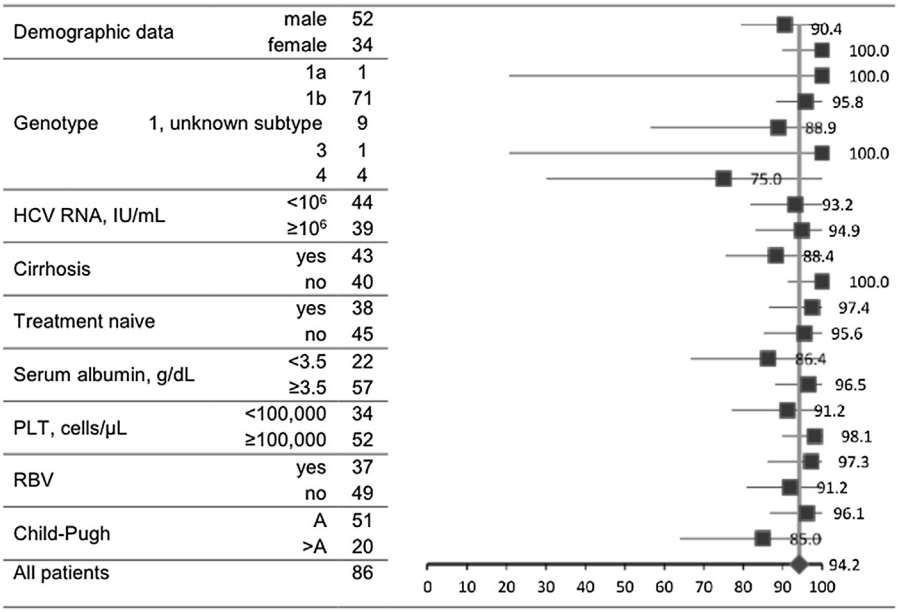

Fig. 1. SVR12 rates across subgroups, n = 86; some measures do not count up to 86 due to missed baseline data in few patients, lines demonstrate 95% confidence intervals. HCV RNA, hepatitis C virus ribonucleic acid; PLT, platelet count; RBV, ribavirin.

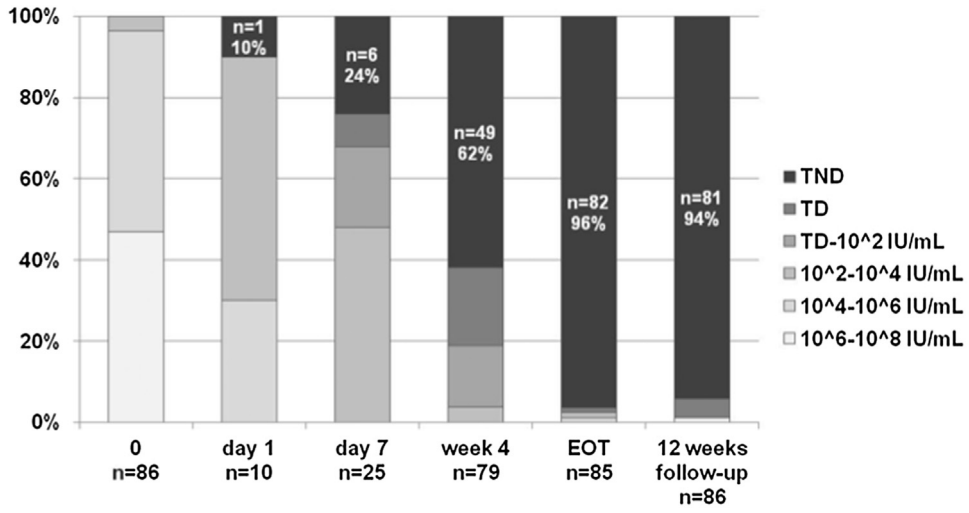

Fig. 2. Virologic response during treatment and follow-up. TND, HCV RNA undetectable; TD, HCV RNA detectable but not quantifiable.

demonstrated that shorter regimens are effective options for HCV genotype 1b-infected, treatment-naïve patients, with a low degree of fibrosis (F0-F2), irrespective of baseline viral load. Our findings are similar to those of large, international trials. Specifically, SVR12 of 97–99% was reported in a group of 1956 HCV genotype 1-infected patients from the German Hepatitis C-Registry treated with LDV/SOF for 8 or 12 weeks [20]. Real-world data from the Spanish HEPA-C Cohort also confirm these findings, with an interim analysis of 86 HCV genotype 1-infected, treatment-naïve, non-cirrhotic patients with baseline HCV RNA of ≤6 million IU/mL revealing SVR12 of 98% for an 8-week regimen [21]. The results of two real-world trials of 8- and 12-week LDV/SOF (HCV-TARGET, TRIO) regimens demonstrated efficacy comparable to that observed in the ION-3 trial [17]. Real-world evidence published to date, suggest an 8-week LDV/SOF regimen is underused, as compared to a 12-week regimen, despite its favorable virologic outcomes in previously untreated HCV genotype 1-infected patients without cirrhosis and high SVR12 rates. The sample size of 8-weeks regimen in our study was too small to make a conclusion but it support use of shortened therapy in patients with less advanced hepatic fibrosis.

Our analysis demonstrates moderate variation in virologic response across subgroups. The highest SVR12 rate was achieved in females patients (100%) and non-cirrhotic patients (100%). In a small Phase 2 study (ELECTRON-2), treatment-experienced patients who received LDV/SOF ± RBV for 12 weeks had an SVR12 of 82% [22]. Similarly to the high virologic responses observed in HCV genotype 1b-infected patients, high SVR12 rates in non-cirrhotic patients are in line with previous clinical trials of LDV/SOF ± RBV [11–13]. In our study, the lowest SVR12 rates (<90%) were observed in cirrhotic patients with serum albumin levels of <3.5 g/dL, and patients with Child-Pugh class B or C; this finding is consistent with previously published studies of LDV/SOF. A similar SVR rate (88%) was recently demonstrated in a large cohort of patients from the US Veterans Administration register [23]. A lower SVR rate in cirrhotic patients (85%) treated with LDV/SOF for 12 weeks without RBV was also confirmed by Curry et al. [24] in a comparative analysis of registration and real-world studies. Our study confirms LDV/SOF ± RBV is generally well tolerated. Although AEs were frequently reported, most were mild and transient. Anemia and hyperbilirubinemia were mainly reported in the RBV-treated group.

The major limitation of our study is the relatively small sample size, which resulted in a small number of patients in the analyzed subgroups; consequently, the effectiveness of treatment in patient subpopulations may be misestimated. The results of our study should be interpreted carefully and further research is necessary to confirm our findings. Results of the HARVEST study are in line with previous LDV/SOF ± RBV studies, including both randomized controlled trials and real-world studies.

Table 4
Clinical and laboratory adverse events, n (%).

	RBV+ n = 37	RBV- n = 49	All n = 86
All AEs	29 (78.4)	40 (81.6)	69 (80.2)
Fatigue/asthenia	8 (21.6)	11 (22.4)	19 (22.1)
Headache	5 (13.5)	8 (16.3)	13 (15.1)
Arthralgia	2 (5.4)	4 (8.2)	6 (7.0)
Cough	3 (8.1)	0 (0.0)	3 (3.5)
Diarrhea	2 (5.4)	0 (0.0)	2 (2.3)
Edema	2 (5.4)	0 (0.0)	2 (2.3)
Serious AEs	3 (8.1)	0 (0.0)	3 (3.5)
Ascites	1 (2.7)	0 (0.0)	1 (1.2)
Sepsis	1 (2.7)	0 (0.0)	1 (1.2)
Variceal bleeding	1 (2.7)	0 (0.0)	1 (1.2)
Anemia (Hb <10 g/dL)	6 (16.2)	1 (2.0)	7 (8.1)
Hyperbilirubinemia (>3 mg/dL)	3 (8.1)	0 (0.0)	3 (3.5)

Only AEs present in ≥2% of patients (any group) are shown. AEs, adverse events; Hb, hemoglobin.

Declaration of funding interests

The HARVEST study was investigator-initiated and independent, but medication was provided, free of charge, by Gilead Poland.

In summary, our findings confirm that treatment with LDV/SOF ± RBV is an effective and safe option for patients with HCV infection, including those with advanced liver disease and a history of non-response to PEG-IFN-based therapy. The high SVR12 rates observed in our study are similar to previous registration studies of LDV/SOF ± RBV. No unexpected AEs were observed.

Conflict of interest and disclosure statement

R. Flisiak has served as a consultant and has presented sponsored lectures for AbbVie, BMS, Gilead, Janssen, Merck and Roche. M. Łucejko has presented sponsored lectures for Gilead and Abbvie. A. Piekarska has served as a consultant and has presented

sponsored lectures for AbbVie, BMS, Gilead, Merck and Roche. K. Sikorska has presented sponsored lectures for Abbvie, Gilead, BMS and Roche. R. Pleśniak has presented sponsored lectures for Abbvie, BMS, Gilead and Roche. I. Mozer-Lisewska has no personal interests to declare. M. Wawrzynowicz-Syczewska has presented sponsored lectures for Gilead, BMS and Abbvie. D. Kozielewicz has presented sponsored lectures for AbbVie, BMS, Roche and Gilead. D. Zarębska-Michaluk has presented sponsored lectures for AbbVie, Gilead, MSD, BMS and Roche. K. Simon has served as a consultant and has presented sponsored lectures for Roche, Gilead, BMS, Abbvie, MSD, Janssen, Alfa Wasserman and Baxter. E. Janczewska has served as a consultant for AbbVie, BMS, Gilead and Janssen, and has presented sponsored lectures for AbbVie, BMS, Gilead, Janssen, MSD and Roche. A. Garlicki has served as a consultant for Abbvie, BMS, Gilead, Glaxo, Janssen, MSD and Roche, and has presented sponsored lectures for Abbvie, BMS, Gilead, Glaxo, Janssen, MSD, Merz, Novartis, Roche and Sanofi.

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