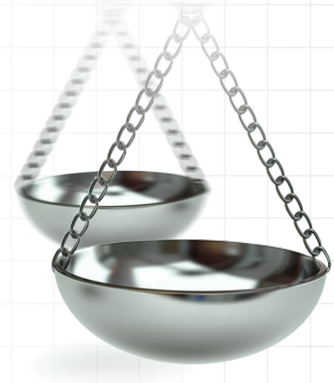
Short Communication



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Comparative effectiveness of pan-genotypic therapies for the treatment of patients with hepatitis C virus infection in Bulgaria

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Hepatitis C virus (HCV) is a positive-stranded RNA virus which belongs to the family of *Flaviviridae*, predominantly infecting liver hepatocytes. HCV infection is a major cause for morbidity worldwide. **Aim:** The primary objective was to evaluate the comparative effectiveness of pan-genotypic therapies for the treatment of patients with HCV infection in Bulgaria. **Materials & methods:** The databases MEDLINE, EMBASE, Cochrane Library, PubMed and clinicaltrials.gov were searched to identify studies evaluating the therapeutic efficacy of sofosbuvir/velpatasvir/voxilaprevir, sofosbuvir/velpatasvir and glecaprevir/pibrentasvir for the treatment of HCV patients. **Results:** The range of sustained virologic response rates among all genotypes achieved after therapy with sofosbuvir/velpatasvir/voxilaprevir was 92–100% (8-week therapy) in treatment-naive patients and 99–100% (12-week therapy) in experienced patients. The range of sustained virologic response rates with glecaprevir/pibrentasvir was 91–100% (12-week therapy) and 97–100% (12-week therapy) with sofosbuvir/velpatasvir. **Conclusion:** Sofosbuvir/velpatasvir/voxilaprevir is a noninferior therapy offering a simple and short-term treatment regimen with high efficacy, favorable safety profile and good tolerability.

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Keywords: Bulgaria • comparative effectiveness • HCV • hepatitis C virus • treatment

Hepatitis C virus (HCV) is a positive-stranded RNA virus which belongs to the family of *Flaviviridae*, predominantly infecting liver hepatocytes [1]. HCV infection is a major cause for morbidity worldwide. As of 2016, 158 million people (2%) worldwide were infected with hepatitis C [2]. Chronic HCV infection is a leading cause of complications from chronic liver disease, including cirrhosis, liver failure, hepatocellular carcinoma and death [3,4]. In 2017, 84 persons (49 men and 35 women) were infected with HCV in Bulgaria (incidence 1.18), with the highest incidence observed in the 60–64 age group (2.43, 12 new cases). Of all the persons infected with HCV, 54.76% were in the 50+ group. One death from HCV infection was registered (mortality 0.01, lethality rate 1.19%) [5].

Understanding the effectiveness of antiviral regimens is critical for making informed decisions for the treatment of HCV infection. Treatment of HCV infection has been revolutionized in the last few years by the introduction of highly effective direct-acting antivirals (DAAs), with which we might finally have the potential to treat the infection and not just the disease. DAAs are able to achieve >90% rates of sustained virologic response (SVR) in patients with more advanced liver disease, as well as to further improve the management of HCV patients with prior treatment failure or with severe renal impairment. Treatment with new pan-genotypic regimens can be initiated without knowledge of the genotype and subtype in areas where genotype determination is not available and/or not affordable, or to simplify treatment access [6]. Moreover, these drugs are better tolerated and have more convenient once daily dosing regimens with shorter treatment schedules. However, some types of patients will

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remain 'difficult to treat', such as: DAAs-experienced patients with resistance-associated variants (RAVs), patients with decompensated cirrhosis (DCC) and genotype 3 cirrhotic patients [7].

Aim

The primary objective of this study was to evaluate the comparative effectiveness of pan-genotypic therapies for the treatment of patients with HCV infection in Bulgaria (sofosbuvir/velpatasvir/voxilaprevir, sofosbuvir/velpatasvir and glecaprevir/pibrentasvir).

Materials & methods

The databases MEDLINE, EMBASE, Cochrane Library, PubMed and clinicaltrials.gov were searched to identify studies evaluating the therapeutic efficacy of sofosbuvir/velpatasvir/voxilaprevir, sofosbuvir/velpatasvir and glecaprevir/pibrentasvir for the treatment of HCV in treatment-naive/-experienced patients with genotypes GT1/2/3/4/5/6. The search was held using the following keywords: HCV, sofosbuvir/velpatasvir/voxilaprevir, sofosbuvir/velpatasvir, glecaprevir/pibrentasvir, clinical trials, comparative, study. The research was mainly focused on the comparison of SVR in patients with genotype GT1b, since according to local epidemiological data, 90% of HCV-positive patients in Bulgaria are carriers of this genotype.

Results

The systematic literature review identified 11 studies which evaluated the efficacy of pan-genotypic treatments. The range of SVR rates among all the genotypes achieved after therapy with sofosbuvir/velpatasvir/voxilaprevir was 92–100% (8-week therapy) in treatment-naive patients and 99–100% (12-week therapy) in experienced patients, 91–100% (12-week therapy) with glecaprevir/pibrentasvir and 97–100% (12-week therapy) with sofosbuvir/velpatasvir. The highest SVR rates for patients with GT1b genotype was achieved in treatment-experienced patients receiving 12-week therapy with sofosbuvir/velpatasvir/voxilaprevir (99%).

Overall, treatment with sofosbuvir/velpatasvir/voxilaprevir for 8 or 12 weeks demonstrated high SVR rates of 95–97.3% across all trials and HCV genotypes [8,9]. The results from the clinical trials POLARIS-1, POLARIS-2, POLARIS-3 and POLARIS-4 are presented in Table 1. Sofosbuvir/velpatasvir/voxilaprevir proved an effective treatment option for patients historically associated with poorer response to treatment including those with cirrhosis, prior treatment failure or presence of NS5A RAVs. Across the POLARIS trials, these patients achieved high SVR12 rates comparable to those in patients with more favorable patient characteristics associated with the ability to achieve SVR.

Treatment with sofosbuvir/velpatasvir/voxilaprevir for 8 or 12 weeks was well tolerated in patients with HCV. The incidence and severity of AEs following treatment with sofosbuvir/velpatasvir/voxilaprevir was similar to patients treated with sofosbuvir/velpatasvir or placebo [8].

The results for the therapeutic efficacy of sofosbuvir/velpatasvir/voxilaprevir and glecaprevir/pibrentasvir measured by SVR12 are presented and compared side by side. Regarding the final conclusions being drawn, the results should be interpreted with caution.

The SVR12 results for sofosbuvir/velpatasvir/voxilaprevir and glecaprevir/pibrentasvir are presented in Table 2.

Discussion

Antiviral therapy for chronic HCV infection is still evolving. The introduction of new DAAs, especially the launch of sofosbuvir, has substantially altered the HCV treatment landscape. SVR is the primary outcome for evaluating comparative effectiveness.

Currently, sofosbuvir/velpatasvir is the only pan-genotypic treatment for HCV approved in Bulgaria that is approved by the European Medicines Agency and the Food and Drug Administration (in 2016). It provides an opportunity to achieve a 100% cure and is also highly effective in difficult-to-treat patients, including those with GT 3 and DCC, in addition with RBV.

Sofosbuvir/velpatasvir/voxilaprevir is a 12-week pan-genotypic, single-tablet regimen specifically designed to cure the majority of DAA-experienced patients, including those who have received an NS5A-containing regimen. SOF/VEL/VOX offers an 8-week regimen in DAA-naive noncirrhotic patients and a 12-week regimen in DAA-naive patients with compensated cirrhosis, with cure rates up to 100%.

Table 1. Results from POLARIS-1, POLARIS-2, POLARIS-3 and POLARIS-4 clinical trials.

	NCT02607800 POLARIS-2 (GS-US-367-1172) [8,10]	NCT02639338 POLARIS-3 (GS-US-367-1173) [11,12]	NCT02607735 POLARIS-1 (GS-US-367-1171) [10]	NCT02639247 POLARIS-4 (GS-US-367-1170) [13]
Primary end points				
Therapy	Sof/vel/vox 8 weeks; sof/vel 12 weeks	Sof/vel/vox 8 weeks; sof/vel 12 weeks	Sof/vel/vox 12 weeks*	Sof/vel/vox 12 weeks; sof/vel 12 weeks
SVR12	476/501 (95%); 432/440 (98.2%)	106/110 (96.4%); 105/109 (96.3%)	253/263 (96.2%)	177/182 (97.3%); 136/151 (90.1%)
Secondary end points				
SVR12				
Cirrhosis:				
Present	82/90 (91%); 83/84 (99%)	–	113/121 (93%)	81/84 (96%); 59/69 (86%)
Absent	394/411 (96%); 349/356 (98%)	–	140/142 (99%)	96/98 (98%); 77/82 (94%)
Prior treatment:				
Naive	–	72/75 (96%); 76/77 (99%)	–	–
Experienced	–	34/35 (97%); 29/32 (91%)	–	–
Genotype:				
Overall	476/501 (95%); 432/440 (98%)	–	–	–
GT1	217/233 (93%); 228/232 (98%)	–	146/150 (97%)	–
GT1a	155/169 (92%); 170/172 (99%)	–	97/101 (96%)	53/54 (98%); 39/144 (89%)
GT1b	61/63 (97%); 57/59 (97%)	–	45/45 (100%)	23/24 (96%); 21/22 (95%)
GT2	61/63 (97%); 53/53 (100%)	–	5/5 (100%)	31/31 (100%); 32/33 (97%)
GT3	91/92(99%); 86/89 (97%)	–	74/78 (95%)	51/54 (94%); 44/52 (85%)
GT4	58/63 (92%); 56/57 (98%)	–	20/22 (91%)	19/19 (100%); 0
GT5	17/18 (94%); 0	–	1/1 (100%)	–
GT6	30/30 (100%); 9/9 (100%)	–	6/6 (100%)	–
Unknown	2/2 (100%); 0	–	–	–
Baseline RAV:				
No RAV	223/230 (97%); 206/211 (98%)	80/84 (95%); 76/80 (95%)	42/43 (98%)	85/86 (99%); (89.3%)
RAV	234/251 (93%); 217/220 (99%)	23/23 (100%); 23/23 (100%)	199/205 (97%)	83/83 (100%); (90%)
Safety profile	sof/vel/vox 8 weeks; sof/vel 12 weeks	sof/vel/vox 8 weeks; sof/vel 12 weeks	sof/vel/vox 12 weeks*	sof/vel/vox 12 weeks; sof/vel 12 weeks
All AE	361 (72.1%); 303 (68.9%)	83 (75.5%); 81 (74.3%)	206 (78.3%); 107 (70.4%)	140 (76.9%); 111 (73.5%)
Treatment-related AE	253 (50.5%); 182 (41.4%)	60 (54.5%); 51(46.8%)	145 (55.1%); 63 (41.4%)	106 (58.2%); 77 (51.0%)
AE grade ≥3	11 (2.2%); 6 (1.4%)	3 (2.7%); 4 (3.7%)	5 (1.9%); 4 (2.6%)	2 (1.1%); 2 (1.3%)
Treatment-related AE grade ≥3	1 (0.2%); 0	0; 2 (1.8%)	1 (0.4%); 0	0; 0
SAE	15 (3.0%); 7 (1.6%)	2 (1.8%); 3 (2.8%)	5 (1.9%); 7 (4.6%)	4 (2.2%); 4 (2.6%)
Treatment-related SAE	0; 0	0; 0	0; 0	0; 0
AE leading to withdrawal	0; 2 (0.5%)	0; 1 (0.9%)	1 (0.4%); 3 (2.0%)	0; 1 (0.7%)
AE leading to treatment discontinuation	1 (0.2%); 2 (0.5%)	1 (0.9%); 0	0; 1 (0.7%)	1 (0.5%); 0
Death	0; 0	1 (0.9); 0	0; 0	1 (0.5%); 0
Most common AE (%):				
Headache	19.4; 17.3	19.1; 22.0	20.9; 13.8	23.1; 22.5
Fatigue	16.0; 13.0	20.0; 13.8	17.5; 15.1	19.2; 22.5
Diarrhea	13.2; 3.6	13.6; 2.8	13.3; 9.2	13.7; 2.6
Nausea	12.0; 7.3	19.1; 6.4	12.5; 6.6	10.4; 3.3
Asthenia	–	–	6.1; 3.9	4.4; 6.0
Insomnia	–	–	6.1; 3.3	–
Irritability	–	–	–	2.2; 5.3

*None of the patients who received placebo in POLARIS-1 had an HCV RNA level of less than 15 IU per ml at any time point.
AE: Adverse event; GT: Genotype; IU: International unit; HCV: Hepatitis C virus; RAV: Resistance-associated variant; SAE: Serious adverse event; sof: Sofosbuvir; SVR: Sustained virologic response; vel: Velpatasvir; vox: Voxilaprevir.

Table 2. SVR12 results for sofosbuvir/velpatasvir/voxilaprevir and glecaprevir/pibrentasvir.

	Sofosbuvir/velpatasvir/voxilaprevir				Glecaprevir/pibrentasvir			
	Untreated	Treated	No cirrhosis	Cirrhosis	Untreated		Treated	
					No cirrhosis	Cirrhosis	No cirrhosis	Cirrhosis
GT1a	92% (155/169) POLARIS-2 + POLARIS-3	97% (150/155) 12 weeks POLARIS-1 + POLARIS-4	99% (140/142) 12 weeks POLARIS-1; 96% (394/411) 8 weeks POLARIS-2; 98% (96/98) 12 weeks POLARIS-4	93% (113/121) 12 weeks POLARIS-1; 91% (82/90) 8 weeks POLARIS-2; 96% (81/84) 12 weeks POLARIS-4	99.7% (351/352) 12 weeks ENDURANCE-1	99% (89/90) 12 weeks Treated + untreated EXPEDITION-1	100% (15/15) * 12 weeks SURVEYOR-1	99% (89/90) 12 weeks Treated + untreated EXPEDITION-1
GT1b	97% (61/63) POLARIS-2 + POLARIS-3	99% (68/69) 12 weeks POLARIS-1 + POLARIS-4						
GT2	97% (61/63) POLARIS-2 + POLARIS-3	100% (36/36) 12 weeks POLARIS-1 + POLARIS-4			99.5% (195/196) 12 weeks Treated + untreated ENDURANCE-2	100% (31/31) 12 weeks Treated + untreated EXPEDITION-1	99.5% (195/196) 12 weeks Treated + untreated ENDURANCE-2	100% (31/31) 12 weeks Treated + untreated EXPEDITION-1
GT3	98% (197/202) POLARIS-2 + POLARIS-3	95% (126/132) 12 weeks POLARIS-1 + POLARIS-4			95.3% (222/233) 12 weeks ENDURANCE-3	98% (39/40) 12 weeks SURVEYOR-2	91% (20/22) 12 weeks SURVEYOR-2	96% (45/47) 16 weeks SURVEYOR-2
GT4	94% (59/63) POLARIS-2 + POLARIS-3	95% (39/41) 12 weeks POLARIS-1 + POLARIS-4			99% (75/76) 12 weeks Treated + untreated ENDURANCE-4	100% (16/16) 12 weeks Treated + untreated EXPEDITION-1	99% (75/76) 12 weeks Treated + untreated ENDURANCE-4	100% (16/16) 12 weeks Treated + untreated EXPEDITION-1
GT5	94% (17/18) POLARIS-2 + POLARIS-3	100% (1/1) 12 weeks POLARIS-1 + POLARIS-4			100% (26/26) 12 weeks Treated + untreated ENDURANCE-4	100% (2/2) 12 weeks Treated + untreated EXPEDITION-1	100% (26/26) 12 weeks Treated + untreated ENDURANCE-4	100% (2/2) 12 weeks Treated + untreated EXPEDITION-1
GT6	100% (30/30) POLARIS-2 + POLARIS-3	100% (6/6) 12 weeks POLARIS-1 + POLARIS-4			100% (19/19) 12 weeks Treated + untreated ENDURANCE-4	100% (7/7) 12 weeks Treated + untreated EXPEDITION-1	100% (19/19) 12 weeks Treated + untreated ENDURANCE-4	100% (7/7) 12 weeks Treated + untreated EXPEDITION-1

*Refers to glecaprevir 200 mg/pibrentasvir 120 mg
GT: Genotype.

Although sofosbuvir/velpatasvir/voxilaprevir is a noninferior compared with both sofosbuvir/velpatasvir and glecaprevir/pibrentasvir in terms of SVR, it was associated with a shorter treatment duration, favorable safety profile and good tolerability.

For the assessment of the comparative therapeutic effectiveness assessment of sofosbuvir/velpatasvir/voxilaprevir versus the alternative glecaprevir/pibrentasvir no comparison could be made as there are no direct comparisons. The literature search did not identify a meta-analysis or a general comparator so that an indirect comparison to be made. This is considered as a limitation of the analysis.

Additional research would help clarify the comparative effectiveness of antiviral HCV treatments, especially head-to-head trials. Studies are needed to further understand the long-term clinical outcomes associated with different antiviral treatments, the long-term and the comparative effectiveness of triple therapy and effective strategies to improve adherence [14]. Other antiviral agents are in active development and expected to be accessible within the next few years.

Conclusion

The SVR12 rate in patients receiving sofosbuvir/velpatasvir/voxilaprevir for 8 weeks is comparable to both sofosbuvir/velpatasvir and glecaprevir/pibrentasvir treatments for 12 weeks, thus demonstrating that sofosbuvir/velpatasvir/voxilaprevir is a noninferior therapy offering simple (administration once daily) and a short-term (8-week) treatment regimen with high efficacy, favorable safety profile and good tolerability. This would

result in improving the quality of life of patients and contribute significantly to the treatment of HCV infection in Bulgaria.

Summary points

- In 2017, 84 persons were infected with Hepatitis C virus (HCV) in Bulgaria (incidence 1.18), with the highest incidence observed in the 60–64 age group (2.43), and one death from HCV infection was registered.
- Sofosbuvir/velpatasvir/voxilaprevir is a noninferior therapy offering a simple and short-term treatment regimen with high efficacy, favorable safety profile and good tolerability.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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