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Hepatitis C Treatment: What to Expect in 2017

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Abstract: *Hepatitis C virus infection is a substantial health problem on a global scale. (1) It is estimated that approximately 185 million people live with hepatitis C worldwide, with 350,000–500,000 patients dying each year from liver disease associated with hepatitis C. (2) However, something is about to change. In the latest years, there has been a shift in treatment paradigm due to the discovery and approval of direct-acting antiviral agents. (3) Nevertheless, these regimens still included ribavirin, which increased side effects, cost, and inconvenience of treatment. Moreover, improved treatment options for patients who did not respond to prior direct-acting antiviral agents (and may have drug-resistant virus) and for hepatitis C virus genotype 3 infection, with or without cirrhosis, were desirable. Thus, three new promising direct-acting antiviral agents were developed to fulfill these significant unmet medical needs. (4,5)*

In many countries, sustainability has been the buzzword across all stakeholders. Still, direct-acting antiviral agents have demonstrated a favorable cost-effectiveness profile (6) and their exceptional cure rates have already helped establish the concept that chronic hepatitis C virus infection can be cured in most, if not all, affected individuals.

This review summarizes the clinical potential of velpatasvir-sofosbuvir, velpatasvir-voxilaprevir-sofosbuvir and glecaprevir-pibrentasvir, discussing key results and future directions. Its aim is to highlight the significance of a future free from hepatitis C.

Keywords: *Hepatitis C virus, direct-acting antiviral agents, sustained virologic response, cure, difficult-to-treat populations*

Abbreviations

Hepatitis C virus – HCV
Hepatocellular carcinoma – HCC
Sustained Virologic Response – SVR
Interferon – IFN
Ribavirin – RBV
Direct-acting antiviral agents – DAAs
Sofosbuvir – SOF
Velpatasvir – VEL
Voxilaprevir – VOX

1. INTRODUCTION

The Hepatitis C virus (HCV) is a small-enveloped virus of the Flaviridae family and genus Hepacivirus, (7) with a single-stranded positive RNA molecule of approximately 9.6 kb. (8) Prior to the discovery of the viral agent, HCV was mainly transmitted via blood products. Since then, injection drug use has arisen as the major mode of transmission in developed countries. (2)

The main problem is that, following exposure to HCV, only a minority of patients clears the acute infection, whereas 80% persist with life-long chronic viremia. (9) Chronic HCV infection is a serious, progressive, and potentially life-threatening disease. (10,11) If left untreated, over time it can cause liver damage or failure due to the development of cirrhosis. This liver complication can lead patients at substantial risk of decompensated disease and hepatocellular carcinoma (HCC), (12) which impose a considerable burden on affected people, healthcare systems and society. (13,14) Early diagnosis could help prevent these consequences, but HCV infection is often undiagnosed because it is usually asymptomatic during decades and so, the majority of HCV-infected individuals are unaware of their infection. (15)

The goal of treatment in all infected individuals, regardless of which of the six major genotypes are present, remains the achievement of a sustained virologic response (SVR) in which circulating HCV RNA is undetectable (with the use of a highly sensitive assay) following treatment. When a SVR is achieved, there is a 99% chance that the hepatitis C infection is cured. (13,16) Historically, SVR was defined as HCV RNA levels below a designated threshold of quantification 24 weeks after completion of treatment (SVR24). (17) However, more recent data shows that viral clearance 12 weeks post-treatment (and sometimes, even 8 weeks) correlates closely to SVR24. (18) Therefore, an undetectable HCV RNA at 12 weeks after treatment (SVR12) is considered an appropriate primary efficacy endpoint (19) and translates into "cure" for nearly all patients. (13)

2. DIRECT-ACTING ANTIVIRAL AGENTS VERSUS INTERFERON-BASED THERAPIES

The new regimens for HCV mean a breakthrough novelty in the history of anti-HCV treatment. Previous treatments for HCV were often long and difficult. Many lasted from 24 to 48 weeks and showed suboptimal efficacy in viral response with a range of commonly occurring significant side effects, which impaired therapeutic compliance. (20) Nowadays, HCV patients can benefit from a less complex administration schedule and expect interferon (IFN) and even ribavirin (RBV)-free combinations. This results in a reduction of the incidence and severity of adverse events, optimizing quality of life during therapy and improving adherence to direct-acting antiviral agents (DAAs).

3. SOFOSBUVIR-VELPATASVIR

Sofosbuvir-velpatasvir (EPCLUSA®) is a prescription medicine used to treat adults with chronic (lasting a long time) hepatitis C genotype 1, 2, 3, 4, 5, or 6 infection with or without cirrhosis (compensated). In clinical studies, sofosbuvir-velpatasvir (SOF-VEL) had high overall cure rates. (Table 1) The most common side effects were headache and tiredness. (21)

Table 1. *Summary of clinical studies of sofosbuvir-velpatasvir.*

Clinical Study (Reference)	Number of patients (% cirrhosis)	HCV genotype (%)	Treatment History	SVR12 by Genotype, Cirrhosis and Treatment Experience		
ASTRAL-1 (22)	740 (19%)	1 2 4 5 6	Treatment-naïve and treatment-experienced	SOF - VEL, 12 weeks	Genotype 1a	98% (206/210)
					Genotype 1b	99% (117/118)
					Genotype 2	100% (104/104)
					Genotype 4	100% (116/116)
					Genotype 5	97% (34/35)
					Genotype 6	100% (41/41)
					Without Cirrhosis	99% (496/501)
					With Cirrhosis	99% (120/121)
					Treatment-naïve	99% (418/423)
					Treatment-experienced	99% (200/201)
ASTRAL-2 (23)	266 (14%)	2 (100%)	Treatment-naïve and treatment-experienced	SOF - VEL, 12 weeks	Treatment-naïve without cirrhosis	99% (99/100)

				SOF + RBV, 12 weeks	Treatment-naïve without cirrhosis	96% (92/96)
				SOF - VEL, 12 weeks	Treatment-naïve with cirrhosis	100% (15/15)
				SOF + RBV, 12 weeks	Treatment-naïve with cirrhosis	93% (14/15)
				SOF - VEL, 12 weeks	Treatment-experienced without cirrhosis	100% (15/15)
				SOF + RBV, 12 weeks	Treatment-experienced without cirrhosis	81% (13/16)
				SOF - VEL, 12 weeks	Treatment-experienced with cirrhosis	100% (4/4)
				SOF + RBV, 12 weeks	Treatment-experienced with cirrhosis	100% (4/4)
ASTRAL-3 (23)	552 (30%)	3 (100%)	Treatment-naïve and treatment-experienced	SOF - VEL, 12 weeks	Treatment-naïve without cirrhosis	98% (160/163)
				SOF + RBV, 24 weeks	Treatment-naïve without cirrhosis	90% (141/156)
				SOF - VEL, 12 weeks	Treatment-naïve with cirrhosis	93% (40/43)
				SOF + RBV, 24 weeks	Treatment-naïve with cirrhosis	73% (33/45)
				SOF - VEL, 12 weeks	Treatment-experienced without cirrhosis	91% (31/34)
				SOF + RBV, 24 weeks	Treatment-experienced without cirrhosis	71% (22/31)
				SOF - VEL, 12 weeks	Treatment-experienced with cirrhosis	89% (33/37)

				SOF + RBV, 24 weeks	Treatment-experienced with cirrhosis	58% (22/38)

In patients with advanced cirrhosis (decompensated), this combination is used with RBV. (21) ASTRAL-4 assessed the efficacy and safety of SOF-VEL in patients with genotype 1 to 6 chronic HCV with decompensated cirrhosis; whereas ASTRAL-5 evaluated safety and efficacy of SOF-VEL in patients coinfected with HCV and HIV-1. (Table 2) (24,25)

Table 2. *Summary of clinical studies of sofosbuvir-velpatasvir in special populations*

Clinical Study (Reference)	Number of patients (% cirrhosis)	HCV genotype (%)	Treatment History	SVR12 by Genotype, Cirrhosis status and Treatment history		
ASTRAL-4 (24)	267	1 2 3 4 5 6	Treatment-naïve and treatment-experienced	SOF - VEL, 12 weeks	Genotype 1	88% (60/68)
					Genotype 3	50% (7/14)
					Genotypes 2,4 and 6	100% (8/8)
				SOF - VEL + RBV, 12 weeks	Genotype 1	96% (65/68)
					Genotype 3	85% (11/13)
					Genotypes 2,4 and 6	100% (6/6)
				SOF - VEL, 24 weeks	Genotype 1	92% (65/71)
					Genotype 3	50% (6/12)
					Genotypes 2,4 and 6	86% (6/7)
ASTRAL-5 (25)	106 (18%)	1 (74%) 2 (10%) 3 (11%) 4 (5%)	Treatment-naïve and treatment-experienced	SOF - VEL, 12 weeks	Genotype 1a	95% (62/65)
					Genotype 1b	92% (11/12)
					Genotype 2	100% (11/11)
					Genotype 3	92% (11/12)
					Genotype 4	100% (4/4)
					Without Cirrhosis	94% (80/85)
					With Cirrhosis	100% (19/19)
					Treatment-naïve	93% (71/75)
					Treatment-experienced	97% (28/29)

4. SOFOSBUVIR-VELPATASVIR-VOXILAPREVIR

Four Phase 3 clinical studies (POLARIS-1, POLARIS-2, POLARIS-3 and POLARIS-4) evaluated a once-daily, fixed-dose combination of sofosbuvir (SOF), a nucleotide analog NS5B polymerase inhibitor; velpatasvir (VEL), a pangenotypic NS5A inhibitor; and voxilaprevir (VOX; GS-9857), an investigational pangenotypic NS3/4A protease inhibitor, for the treatment of genotype 1,2,3,4,5 and 6 chronic HCV infection. (Table 3)

Table 3. *Summary of clinical studies of sofosbuvir-velpatasvir-voxilaprevir*

Clinical Study (Reference)	Population	Number of patients (% cirrhosis)	HCV Genotype	Treatment	Duration	SVR12 Rates
POLARIS-1 (26)	Patients who failed prior treatment with an NS5A inhibitor. The most common prior NS5A inhibitors were ledipasvir (55%) and daclatasvir (23%).	415 (41% hadcirrhosis)	1 2 3 4 5 6	SOF-VEL-VOX	12 weeks	96% (253/263)
				Placebo	12 weeks	0% (0/152)
POLARIS-2 (26)	DAA-naïve 23% hadpreviouslyfailedtreatmentwithan IFN-basedregimen.	941 (18% had cirrhosis)	1 2 3 4 5 6	SOF-VEL-VOX	8 weeks	95% (476/501)
				SOF-VEL	12 weeks	98% (432/440)
POLARIS-3 (26)	DAA-naïve 31% hadpreviouslyfailedtreatmentwithan IFN-basedregimen.	219 (100% had cirrhosis)	3	SOF-VEL-VOX	8 weeks	96% (106/110)
				SOF-VEL	12 weeks	96% (105/109)
POLARIS-4 (26)	Patients with prior DAA experience that did not include an NS5A inhibitor. Most patients (85%) had prior DAA experience with SOF.	333 (46% had cirrhosis)	1 2 3 4	SOF-VEL-VOX	12 weeks	97% (177/182)

The most common adverse events among patients who received SOF-VEL-VOX were headache, fatigue, diarrhea and nausea. The overall incidence of adverse events was similar to placebo or SOF-VEL. Among the 1,056 patients who received SOF-VEL-VOX in the four studies, only a patient receiving SOF-VEL-VOX for 12 weeks discontinued due to an adverse event. (26) These results show that this new three-drug co-formulation with different mechanisms of action and high barrier to resistance can provide high cure rates for patients who had previously failed treatment with other DAAs.

5. GLECAPREVIR-PIBRENTASVIR

Glecaprevir-pibrentasvir is an investigational, pan-genotypic regimen that is being evaluated (table 4) not only as a potential cure in 8 weeks for HCV patients without cirrhosis and who are new to treatment, but also in patients with specific treatment challenges, such as genotype 3, patients who were not cured with previous DAA treatment and those with chronic kidney disease, including patients on dialysis.

Table 4. *Summary of clinical studies of glecaprevir-pibrentasvir*

Clinical Study (Reference)	Patient Population	Treatment	Duration	SVR12 Rates
ENDURANCE-1 (27)	Genotype 1 without cirrhosis, naïve or not cured with previous IFN-based treatments (pegIFN +/- RBV or SOF/RBV +/- pegIFN), and patients co-infected with HIV-1.	glecaprevir-pibrentasvir	8 weeks	99% (348/351)

ENDURANCE-3 (27)	Genotype 3 withoutcirrhosis, naïve.	glecaprevir-pibrentasvir	8 weeks	95% (149/157)
SURVEYOR-II, part 3 (28)	Genotype 3 with compensated cirrhosis and/or prior treatment experience.	glecaprevir-pibrentasvir	8 weeks	96%
SURVEYOR-II, part 4 (27)	Genotypes 2, 4, 5, 6 without cirrhosis, naïve or not cured with previous IFN-based treatments (pegIFN, SOF/RBV or pegIFN/SOF).	glecaprevir-pibrentasvir	8 weeks	97% (196/203)
EXPEDITION-4 (29)	Patients with genotypes 1 to 6 chronic HCV infection and stage 4 and 5 CKD, with an eGFR< 30 mL/min/1.73 m2), including 85 patients (82%) who were receiving dialysis at enrollment and 20 patients (19%) who had compensated cirrhosis. It also included patients who were not cured with previous SOF with RBV or IFN with RBV; with or without SOF (44 patients, 42%).	glecaprevir-pibrentasvir	12 weeks	98% (102/104)

This investigational, pan-genotypic regimen of glecaprevir-pibrentasvir is showing to be well tolerated with a favorable safety profile in these difficult-to-treat populations. The most commonly reported adverse events included fatigue and nausea.

6. DISCUSSION

Although the post-marketing phase always requires a careful evaluation of data from the "everyday" clinical practice experience, clinical trials have showed that these new DAA combinations have resolved most issues related to HCV treatment compared with the past regimens. Despite the approval of the first DAAs which have provided high cure rates and simplified treatment for most HCV patients, HCV genotype 3-infected patients with cirrhosis, patients with chronic kidney disease and those who have failed previous treatment with DAAs continued to represent an unmet medical need.

In the era of velpatasvir-sofosbuvir, velpatasvir-voxilaprevir-sofosbuvir and glecaprevir-pibrentasvir, DAA therapy provides a new way to manage these difficult-to-treat HCV-infected patients, who are at a high risk of serious conditions. (30) They are now contemplated and are therefore expected to have a much better prognosis than they have had until very recently. Perhaps, soon, we may no longer have difficult-to-treat populations.

The advent of new generation oral antiviral therapy has led to major improvements in efficacy and tolerability but has also resulted in an explosion of data with increased treatment choice complexity. (31) Thus, clinicians need more detailed, accurate and timely information in order to choose the right regimen for individual patients and educate them. When they counsel and guide their patients, these ones are less likely to be anxious or resistant about taking steps toward possible cure. However, cure does not prevent reinfection and so, it is crucial to advise patients on measures that will reduce their risk (avoid alcohol intake and sexual and injection risk behaviors, eat a balanced diet and take exercise are some examples).

7. CONCLUSION

DAAs have shown that it is possible to minimize the spread of HCV and the morbidity and mortality associated with HCV infection. (32)

Despite the financial controversy around their high costs, which have served as a major barrier for more widespread use, many stakeholders recognize now their long-term cost-benefits and the advantages of a future free from hepatitis C are manifest.

It is true that patients undergoing treatment need systematic monitoring before, during and after therapy, but these new treatment options have offered them hope and re-awakening. It is a clear evolution compared with the previous IFN-based therapies.

8. FUTURE DIRECTIONS

At a future time, treatment failure and resistance can occur and become a clinical challenge to be solved. (30,33)

However, before them, there are already some questions that should concern us. First one is why is the association of RBV with DAAs, in some cases, increasing the SVR12 rate and shortening the duration of treatment? Then, at what point is it no longer worth treating a patient? Will we have the financial capacity to treat reinfected-patients? Will this simplicity of therapeutic regimen encourage risk behaviors in the future?

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