Are we hopefully very close to the end of HCV?

Afdhal N, Reddy KR, Nelson DR, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med 2014; 370: 1483-93.

Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med 2014; 370: 1889-98.

Hepatitis C virus (HCV) infection is a major global health problem that infects about 3% of population worldwide. Development of new direct-acting antiviral agents (DAAs) against the HCV allowed the advance of interferon-free oral therapy regimens that promise to cure more than 90% of genotype 1 patients in previous studies with moderate number of patients (1, 2). The field of HCV therapy is always fresh, always exciting and current trends show that the time of simple treatment regimens with high rates of response and tolerability is very close.

In The New England Journal of Medicine, Nezam Afdhal and colleagues conducted 12 and 24 weeks of treatment with single tablet ledipasvir 90 mg + sofosbuvir 400 mg, with and without ribavirin (1000 mg daily in patients with a body weight <75 kg, and 1200 mg daily in patients with a body weight ≥75 kg) in patients with HCV genotype 1 infection for previously treated (3) and untreated (4) group of patients in different studies. Both studies were phase 3, randomized, open-label and enrolled 440 and 865 patients, respectively.

The studies were designed and conducted according to the protocol by the sponsor (Gilead Sciences) in collaboration with the academic investigators to maintain confidentiality of the data. Genotype 1a subtype and cirrhosis rates in the studies were 79% & 67% and 16% & 20% respectively. The primary end point was sustained virologic response (SVR) at 12 weeks after the end of therapy (Table 1).

Treatment with a once-daily, single tablet regimen of ledipasvir+sofosbuvir therapy resulted in high rates of end of therapy response (ETR) in patients who had not had a SVR to prior interferon based treatment (3) and treatment naive (4) patients. No patient discontinued treatment owing to an adverse event within 12 weeks of the therapies. The SVR rates among cirrhotic patients who were previously treated for HCV were 86% for the 12 weeks of ledipasvir+sofosbusvir therapy group, 82% for the 12 weeks of ledipasvir + sofosbusvir + ribavirin therapy group, 95% for the 24 weeks of ledipasvir+sofosbusvir therapy group and 100% for the 24 weeks of ledipasvir + sofosbusvir + ribavirin therapy group. The presence of cirrhosis did not change any therapy response or safety profile in the treatment naive group study.

The studies also differentiated the adverse events associated with ribavirin including decreased hemoglobin and increased bilirubin consistent with ribavirin-mediated hemolysis. The addition of ribavirin to ledipasvir + sofosbusvir regimen increased toxicity without supplying additional efficacy.

The rates of the response were generally uniform, regardless of baseline viral load, race, subtype difference, IL28B genotype and extend of fibrosis. NS5B S282T variant, which is associated with reduced propensity to sofosbuvir was not detected in these 2 studies (3,4).

There were no control groups in these studies. However common adverse events included fatigue, headache, insomnia, and nausea in ledipasvir + sofosbuvir without ribavirin therapy group were generally similar to those seen in the placebo groups in the past studies.

For the last two decades, dual combination of pegylated interferon and ribavirin therapy was the backbone in HCV therapy. However its success rate has been cited overall around 50% with numerous side effects. Even many patients with psychiatric diseases or cytopenias have been ineligible for the interferon based therapies. Nowadays, we consider not only interferon-free therapy but also ribavirin-free therapy. Combination of

Table 1. Response during and after treatment

		Previously treated HCV patients (3)				Treatment naive HCV patients (4)			
		12 weeks regimen		24 weeks regimen		12 weeks regimen		24 weeks regimen	
		L+S (N=109)	L+S+R (N=111)	L+S (N=109)	L+S+R (N=111)	L+S (N=214)	L+S+R (N=217)	L+S (N=217)	L+S+R (N=217)
HCV RNA <25 IU/mL	At week 2	89 (82)	92 (83)	89 (82)	93 (84)	174/213 (82)	181/217 (83)	179/216 (83)	180/217 (83)
	At week 4	109 (100)	110 (99)	108 (99)	110 (99)	213/213 (100)	215/217 (99)	216/216 (100)	217/217 (100)
	At week 12	108 (99)	111 (100)	109 (100)	110 (99)	213/213 (100)	214/214 (100)	213/214 (>99)	216/216 (100)
	4 week after therapy	103 (94)	107 (96)	109 (100)	110 (99)	211 (99)	213 (98)	215 (99)	215 (99)
	12 week after therapy	102 (94)	107 (96)	108 (99)	110 (99)	211 (99)	211 (97)	212 (98)	215 (99)
Virologic breakthrough		0	0	0	1 (1)	0	0	1	0
Relapse		7 (6)	4 (4)	0	0	1	0	1	0

L: ledipasvir; S: Sofosbuvir; R: Ribavirin; HCV: hepatitis C virus

oral-only, once daily, combined single tablet, ultra short (even as short as 8 weeks) therapy (5) with improved safety, no contraindication, and of course an excellent efficacy is making this therapy unique.

It is still possible that undetectable amounts of virus can be present in the body. The new resistance to antiviral rule is not clear for these effective medications. In addition, HCV has many mutations that cause new resistant variants by DAAs. We do not know which patients need resistance testing. It is obvious that DAAs are absolutely much more effective and less toxic than interferon based therapies. However, it is still unclear whether late relapses may still happen for these new agents.

Finally, the cost of the medications should not limit its access for parts of the world. Recently, Younossi et al. (6) reported oral interferon-free regimen as the most cost-effective therapy by using an analytic Markov model simulating patients until death. Although, the scientist involved in formulating sofosbuvir, Raymond Schinazi, estimates cost at just $1400. A 12 week course of sofosbuvir costs $84000, $1000-a-pill. Gilead says Sovaldi should create significant savings for the healthcare system over time by preventing complications from liver disease and transplants. However, 90% of the patients with HCV infection live in developing or underdeveloped countries, causing difficulty in financing for treatment. Gilead Sciences, facing mounting criticism over the high price of Sovaldi, has offered to supply the medicine to Egypt at a 99% discount compared to the US price. The pharmaceutical firm is offering to sell lower-priced copies of the medication in India as well. Global funding mechanisms can hopefully work as it worked in HIV/AIDS medicines and can ensure DAAs to those patients in need in both underdeveloped and developing countries, as well as those with low income in developed countries.

Veysel Tahan

Department of Gastroenterology, University of Iowa Hospitals and Clinics, Iowa City, IA, USA
DOI: 10.5152/tjg.2014.0009

REFERENCES

1. Lawitz E, Poordad FF, Pang PS, et al. Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): An open-label, randomised, phase 2 trial. Lancet 2014; 383: 515-23. **[CrossRef]**
2. Gane EJ, Stedman CA, Hyland RH, et al. Efficacy of nucleotide polymerase inhibitor sofosbuvir plus the NS5A inhibitor ledipasvir or the NS5B non-nucleoside inhibitor GS-9669 against HCV genotype 1 infection. Gastroenterology 2014; 146: 736-43. **[CrossRef]**
3. Afdhal N, Reddy KR, Nelson DR, et al. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. N Engl J Med 2014; 370: 1483-93. **[CrossRef]**
4. Afdhal N, Zeuzem S, Kwo P, et al. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med 2014; 370: 1889-98. **[CrossRef]**
5. Kowdley KV, Gordon SC, Reddy KR, et al. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. N Engl J Med 2014; 370: 1879-88. **[CrossRef]**
6. Younossi ZM, Singer ME, Mir HM, Henry L, Hunt S. Impact of interferon free regimens on clinical and cost outcomes for chronic hepatitis C genotype 1 patients. J Hepatol 2014; 60: 530-7. **[CrossRef]**