World Journal of Virology

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DOI: 10.5501/wjv.v4.i1.33

World J Virol 2015 February 12; 4(1): 33-35
ISSN 2220-3249 (online)

Ledipasvir and sofosbuvir: Interferon free therapy for hepatitis C virus genotype 1 infection

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Author contributions: Waheed Y solely contributed to this manuscript.
Conflict-of-interest: The author does not have any conflict of interest.

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Telephone: +92-300-5338171
Received: September 1, 2014
Peer-review started: September 2, 2014
First decision: November 19, 2014
Revised: December 3, 2014
Accepted: December 16, 2014
Article in press: December 17, 2014
Published online: February 12, 2015

Abstract

Hepatitis C virus (HCV) has infected more than 200 million people around the globe. From 2001-2011, interferon plus ribavirin remained the standard of care for patients with HCV infection. The therapy had a limited response with a number of side effects. Recently, results for phase III trials of ledipasvir and sofosbuvir combination therapy have been announced. In treatment naïve patients, 12 wk of therapy with ledipasvir and sofosbuvir showed a sustained virological response (SVR) rate of 99%. In treatment experienced patients, 12-24 wk of therapy with ledipasvir and sofosbuvir in the absence or presence of ribavirin showed an SVR rate of 94%-99%. In cirrhotic patients the rate of SVR was 86% and 99% for 12 and 24 wk of therapy, respectively. The ledipasvir and sofosbuvir therapy showed very good results in different subgroups of patients regardless of patient's race, alanine aminotransferase levels, sex and host genetic factors. The combination therapy was well tolerated with no emergence of resistant mutants. The most common adverse effects were nausea, headache and fatigue. With the availability of interferon free therapy with minimal adverse effects, it will be easy to decrease the future morbidity and mortality caused by HCV infection.

Key words: Hepatitis C; Interferon; Ledipasvir; Sofosbuvir; Genotype

Core tip: The interferon based therapy for hepatitis C patients has a limited response with a number of adverse effects. The ledipasvir and sofosbuvir combination therapy showed a sustained virological response (SVR) rate of 99% in treatment naïve patients. The rate of SVR was 94%-99% in treatment experienced patients, while in cirrhotic patients the rate of SVR was 86%-99%. The treatment response was not affected by ethnicity or host genetic factors.

Waheed Y. Ledipasvir and sofosbuvir: Interferon free therapy for hepatitis C virus genotype 1 infection. *World J Virol* 2015; 4(1): 33-35 Available from: URL: http://www.wjgnet.com/2220-3249/full/v4/i1/33.htm DOI: http://dx.doi.org/10.5501/wjv.v4.i1.33

TO THE EDITOR

Hepatitis C virus (HCV) infection is a major health problem around the globe, with more than 200 million people infected worldwide. Although the rate of HCV infection is continuously declining, the rates of HCV associated morbidity and mortality are continuously increasing.

From 2001-2011, interferon and ribavirin therapy remained the standard of care for patients living with HCV. The therapy had a limited response with a number of side effects. The major adverse effects associated with interferon administration were flu like symptoms, cytopenia and depression, whereas ribavirin therapy causes fatigue, anemia, rash and pruritus. The major objective of recent treatment regimens is to eliminate the interferon and ribavirin from the treatment regimen so that the adverse effects of therapy can be reduced and the therapy become available for patients who are ineligible for the interferon and ribavirin therapy.

Sofosbuvir is a nucleoside analogue that can inhibit the HCV polymerase, approved by the Food and Drug Administration for the treatment of patients living with HCV. Ledipasvir is an inhibitor of HCV NS5A protein, showing antiviral activity against HCV genotype 1 infection.

In a phase Ⅱ clinical trial, 100 patients with HCV genotype 1 infection who were treatment naïve or previously treated with protease inhibitors were enrolled at a centre in the United States. The patients were given a fixed-dose combination of sofosbuvir (400 mg) and ledipasvir (90 mg). In cohort A, 60 treatment naïve, non-cirrhotic patients who were given sofosbuvir plus ledipasvir (8 wk), sofosbuvir plus ledipasvir along with ribavirin (8 wk), or sofosbuvir plus ledipasvir (12 wk) showed an SVR rate of 95%, 100%, and 95% respectively. In cohort B, 40 previous non-responders to protease therapy were included. They were given sofosbuvir plus ledipasvir (12 wk) or sofosbuvir plus ledispavir along with ribavirin (12 wk), and the sustained virological response (SVR) rate was 95% and 100%, respectively[1]. The sofosbuvir-ledipasvir combination therapy cured most of patients with HCV genotype 1 infection, irrespective of their treatment history. Further investigations were required to optimize the treatment duration and the role of ribavirin in treatment response.

In a phase Ⅲ clinical trial, 865 previously untreated patients were enrolled and they were randomly divided into four groups. Group 1 received ledipasvir and sofosbuvir for 12 wk and showed an SVR rate of 99%. Group 2 received ledipasvir and sofosbuvir along with ribavirin for 12 wk and showed an SVR rate of 97%. Group 3 received ledipasvir and sofosbuvir for 24 wk and showed an SVR rate of 98%. Group 4 received ledipasvir and sofosbuvir along with ribavirin for 24 wk and showed an SVR rate of 99%. The study concluded that the 12 wk therapy with ledipasvir and sofosbuvir was highly effective for patients living with HCV genotype 1 infection. No additional benefit was observed by the addition of ribavirin or by the extension of therapy to 24 wk[2].

In another phase Ⅲ trial, 440 previously treated patients were enrolled, 20% of whom had cirrhosis. The patients were given ledipasvir and sofosbuvir in the presence or absence of ribavirin from 12 or 24 wk. The rate of SVR achieved was 94%-99%. In patients with cirrhosis the rate of SVR was 86% (ledipasvir-sofosbuvir) and 82% (ledipasvir-sofosbuvir plus ribavirin) with 12 wk of treatment, while the rate of SVR was 99% (with both regimens) in patients having 24 wk of treatment. The study concluded that the single tablet of ledipasvir–sofosbuvir showed a better rate of SVR even in the patients who were not responders to the interferon based therapy[3].

The ledipasvir and sofosbuvir therapy produced very good results in different subgroups of patients regardless of patient's race, alanine aminotransferase levels, sex and host genetic factors. The combination therapy was well tolerated. No S282T variant was observed. The most common adverse effects were nausea, headache and fatigue[2-4].

A total of 1952 patients were enrolled in three different phase III trials of ledipasvir and sofosbuvir, out of which 97% showed SVR[2-4]. Out of the remaining 3%, half of them withdrew consent or were lost to follow-up. Undetectable viral RNA was not achieved in only two patients. The rate of relapse was observed in only 2% after stopping therapy. The rate of relapse was also linked with the treatment duration. The rate of relapse was observed in 5%, 2% and 0.2% of patients who received 8 wk, 12 wk and 24 wk of treatment, respectively[5].

With the availability of oral, short duration, interferon free therapy with minimal adverse effects, the future morbidity and mortality associated with HCV infection will decrease. The major problem with the therapy is its cost. The cost of 12 wk therapy with sofosbuvir alone is $84000 and the addition of ledispavir will further increase the cost[5]. The high cost of the therapy will affect the goal of providing safe and effective treatment for millions of patients living with HCV around the globe.

REFERENCES

1 **Lawitz E**, Poordad FF, Pang PS, Hyland RH, Ding X, Mo H, Symonds WT, McHutchison JG, Membreno FE. 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**: 515-523 [PMID: 24209977 DOI: 10.1016/S0140-6736(13)62121-2]

2 **Afdhal N**, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, Romero-Gomez M, Zarski JP, Agarwal K, Buggisch P, Foster GR, Bräu N, Buti M, Jacobson IM, Subramanian GM, Ding X, Mo H, Yang JC, Pang PS, Symonds WT, McHutchison JG, Muir AJ, Mangia A, Marcellin P. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. *N Engl J Med* 2014; **370**: 1889-1898 [PMID: 24725239 DOI: 10.1056/NEJMoa1402454]

3 **Afdhal N**, Reddy KR, Nelson DR, Lawitz E, Gordon SC, Schiff E, Nahass R, Ghalib R, Gitlin N, Herring R, Lalezari J, Younes ZH, Pockros PJ, Di Bisceglie AM, Arora S, Subramanian GM, Zhu Y, Dvory-Sobol H, Yang JC, Pang PS, Symonds WT, McHutchison JG, Muir AJ, Sulkowski M, Kwo P. Ledipasvir and sofosbuvir for previously treated HCV genotype 1 infection. *N Engl J Med* 2014; **370**: 1483-1493 [PMID: 24725238

DOI: 10.1056/NEJMoa1316366]
4 **Kowdley KV**, Gordon SC, Reddy KR, Rossaro L, Bernstein DE, Lawitz E, Shiffman ML, Schiff E, Ghalib R, Ryan M, Rustgi V, Chojkier M, Herring R, Di Bisceglie AM, Pockros PJ, Subramanian GM, An D, Svarovskaia E, Hyland RH, Pang PS, Symonds WT, McHutchison JG, Muir AJ, Pound D, Fried MW. Ledipasvir and sofosbuvir for 8 or 12 weeks for chronic HCV without cirrhosis. *N Engl J Med* 2014; **370**: 1879-1888 [PMID: 24720702 DOI: 10.1056/NEJMoa1402355]
5 **Hoofnagle JH**, Sherker AH. Therapy for hepatitis C--the costs of success. *N Engl J Med* 2014; **370**: 1552-1553 [PMID: 24725236 DOI: 10.1056/NEJMe1401508]

P- Reviewer: Valenti L, Wong DKH **S- Editor**: Ji FF
L- Editor: Wang TQ **E- Editor**: Wu HL

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