Name of journal: *World Journal of Virology*

ESPS Manuscript NO: 13790

Columns: Letter to the Editor

**Ledipasvir and Sofosbuvir: Interferon free therapy for HCV genotype 1 patients**

Waheed Y. Ledipasvir and sofosbuvir for HCV patients

Yasir Waheed

Yasir Waheed, Atta-ur-Rahman School of Applied Biosciences, National University of Sciences and Technology, Islamabad 44000, Pakistan

**Author contributions:** Waheed Y solely contributed to this manuscript.

**Conflict-of-interest:** The author does not have any conflict of interest.

**Open-Access:** This article is an open-access article which selected by an in-house editor and fully peer-reviewed by external reviewers. It distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Correspondence to: Yasir Waheed, PhD,** Atta-ur-Rahman School of Applied Biosciences, National University of Sciences and Technology, H-12, Islamabad 44000, Pakistan. [yasir\_waheed\_199@hotmail.com](mailto:yasir_waheed_199@hotmail.com)

**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:**

**Published online:**

**Abstract**

Hepatitis C virus (HCV) has infected more than 200 million people around globe. From 2001-2011, Interferon plus ribavirin remained the standard of care for HCV patients. The therapy had limited response with 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 therapy of Ledipasvir and Sofosbuvir showed sustained virological response (SVR) of 99%. In treatment experienced patients, 12-24 wk therapy of Ledipasvir and Sofosbuvir in the absence or presence of Ribavirin showed SVR 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, ALT levels, sex and host genetic factors. The combination therapy was well tolerated with no emergence of resistant mutant. 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 hepatitis C infection.

© The Author(s) 2015. Published by Baishideng Publishing Group Inc. All rights reserved.

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

**Core tip:** The Interferon based therapy for hepatitis C patients has limited response with number of adverse effects. The ledipasvir and sofosbuvir combination therapy showed sustained virological response (SVR) of 99% in treatment naïve patients. The rate of SVR was 94%-99% in treatment experience 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 HCV genotype 1 patients. *World J Virol* 2014; In press

**TO THE EDITOR**

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

From 2001-2011, Interferon and ribavirin therapy remained the standard of care for the patients living with HCV. The therapy had limited response with number of side effects. The major adverse effects linked with Interferon administration were flu like symptoms, cytopenia and depression. Whereas ribavirin therapy cause 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 the patients who are ineligible for the Interferon and ribavirin therapy.

Sofosbuvir is a nucleoside analogue of HCV polymerase, approve by FDA for the treatment of patients living with HCV. Ledipasvir is NS5A inhibitor, showed antiviral activity against HCV genotype 1 patients.

In a Phase II clinical trial, 100 HCV genotype 1, treatment naïve or previously treated with protease inhibitors were enrolled at a centre in 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 were given Sofosbuvir plus ledipasvir (8 wk) or Sofosbuvir plus ledipasvir along with ribavirin (8 wk) or Sofosbuvir plus ledipasvir (12 wk) showed SVR of 95%, 100% and 95% respectively. In cohort B, 40 patients, previously non-responders to protease therapy were included. Patients were given Sofosbuvir plus ledipasvir (12 wk) or Sofosbuvir plus ledispavir along with ribavirin (12 wk), showed SVR of 95% and 100% respectively[1]. The Sofosbuvir-ledipasvir combination therapy cured most of HCV genotype 1 patients, irrespective of their treatment history. Further investigations were required to optimize the treatment duration and 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, showed sustained virological response (SVR) of 99%. Group 2 received Ledipasvir and Sofosbuvir along with ribavirin for 12 wk, showed SVR of 97%. Group 3 received Ledipasvir and Sofosbuvir for 24 wk, showed SVR of 98%. Group 4 received Ledipasvir and Sofosbuvir along with Ribavirin for 24 wk, showed SVR of 99%. The study concluded that the 12 wk therapy of Ledipasvir and Sofosbuvir was highly effective for the patients living with HCV genotype 1 infection. No additional benefit was observed by the addition of Ribavirin or by extension of therapy to 24 wk[2].

In another Phase III trial, 440 previously treated patients were enrolled, 20% of which 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 better rates of SVR even in the patients who were not responders to the Interferon based therapy[3].

The Ledipasvir and Sofosbuvir therapy produces very good results in different subgroups of patients regardless of patient’s race, ALT 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].

Total 1952 patients were enrolled in three different Phase III trials of Ledipasvir and Sofosbuvir, out of which 97% showed SVR[2-4]. Out of remaining 3%, half of them withdrew consent or lost from follow up. Undetectable viral RNA was not achieved in only two patients. The rate of relapse was observed only 2% after stopping therapy. The rate of relapse was also linked with the treatment duration. The rate of relapse was observed 5%, 2% and 0.2% in 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 by HCV will decrease. The major problem with the therapy is its cost. The cost of 12 wk therapy of Sofosbuvir alone is $84000 and the addition of Ledispavir will further increase the price[5]. The high price of therapy will affect the goal of providing safe and effective treatment for the millions of patients living with HCV around 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: E-Editor:**