DOI: https://doi.org/10.53350/pjmhs2115123164

ORIGINAL ARTICLE

Efficacy of Sofosbuvir and Daclatasvir in the Treatment of Chronic Hepatits C Viral Infection

MOHAMMAD ARIF[1], SHAH ZAMAN[2], AMIR ZAMAN KHAN[3], RIAZ NASIM[4]
[1]Senior Medical Officer, Rural Health Centre, Kheshgi, District Nowshera
[2,3]Assistant Professors, [4]Head of Department, Department of Pharmacology Peshawar Medical College, Peshawar
*Correspondence **to** Dr. Mohammad Arif, E-mail: arifakhund2018@gmail.comCell: 0335-9733190*

ABSTRACT

Aim: To know the efficacy of combined therapy with sofosbuvir and daclatasvir, in patients suffering from chronic hepatitis C viral infection in Khyber Pakhtunkhwa.
Study Design: Descriptive case series study.
Place and duration of study: Department of Gastroenterology, Hayatabad Medical Complex, Peshawar, Pakistan, from 1stOctober 2017 to 28th February 2019.
Methodology: Ninety eight patients were suffering from chronic hepatitis C infection enrolled. All patients were treated with sofosbuvir 400 mg and daclatasvir 60 mg daily for a period of three to six months. Ribavirin was added to the treatment of patients where indicated. All patients were followed 24 weeks after completion of treatmentto know the outcome in terms of sustained virological response (SVR).
Results: The mean age of patients was 42.16±11.65 years, with 43 males and 55 females. Fifty one patients that received sofosbuvir and daclatasvir, achieved SVR rate of 88.23% (45/51) while 47 patients who were given sofosbuvir, daclatasvir and ribavirin , achieved SVR rate of 89.36 % (42/47). Six months after completing 12 to 24 weeks of treatment, a follow up PCR was done. The SVR rate, 24 weeks post treatment was 88.77% (87/98). The most common side effects observed were generalized body aches 24%, fatigue 21%, headache 10% and fever 6%.
Conclusion: Once daily oral daclatasvir 60mg combined with sofosbuvir 400mg, with or without ribavirin proved effective, with SVR rate of 88.77%, in patients infected with chronic hepatitis C viral infection.
Keywords: Direct acting antiviral, Chronic hepatitis C, Sustained virological response, Ribavirin, Efficacy, Sofosbuvir,

INTRODUCTION

Hepatitis, in which the liver gets inflammed is basically caused by different types of viruses. Acute cases of hepatitis C usually resolve well within a six-month period but in majority of people (up to 85%) the infection moves into a long-lasting stage, called chronic hepatitis[1,2].

Chronic hepatitis C viral infection is an alarming health issue in Pakistan. According to a national survey, conducted in 2007-2008, about 4.8% of population was affected with hepatitis C in Pakistan[3].

Therapeutic use of conventional and pegylated interferon resulted in limited efficacy along with various side effects and prolonged duration of treatment. That was the reason which led to introduction of new therapeutic drugs which showed better sustained virological response (SVR) rate and less adverse effects. In the past few years, scientists were trying to understand and study the life cycle of hepatitis C virus, and the key role played by viral proteins like NS3/NS4A protease, NS5B polymerase, and NS5A replication complex. As a result specific medications targeting these viral proteins were developed[4].

Since 2007, several oral, direct acting anti-HCV agents have been developed. With introduction of these new drugs, patients experience less side effects and better SVR rate while the treatment course is also short (8 to 24 weeks). The combined use of sofosbuvir and daclatasvir, with or without ribavirin, is recommended by American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver recommendations for the treatment of chronic hepatitis C infected patients with genotype-3[2].

The drug sofosbuvir was first used in humans in 2010. Sofosbovir and ribavirin combination was approved by FDA in 2013 to be used for the treatment of HCV genotypes 2 and 3, while peg interferon alfa-2a is added to sofosbuvir and daclatasvir in treatment-naive patients with genotypes 1 and 4[5].

Daclatasvir was introduced for the first time in 2010 by scientists at Bristol-Myers Squibb. In 2014, it was approved for use in Europe and in 2015 in India and America (USA). The use of daclatasvir with other antiviral drugs like sofosbuvir, ribavirin, and interferon is recommended in patients with HCV genotype 1, 2, 3 and 4, as daclatasvir when used alone, is not effective. Daclatasvir directly inhibits NS5A, which is required for the replication of hepatitis C viral RNA and virion assembly. It inhibits activity of the NS5A protein by binding to the N-terminus of NS5A. Inhibition of NS5A protein leads to disruption of hepatitis C RNA production and so viral replication process is stopped.[6]

Sofosbuvir (400mg) and daclatasvir (60mg) with or without ribavirin for a period of 12 to 24 weeks is considered a best treatment choice in patients suffering from chronic HCV infection, including cirrhotic and treatment-experienced patients. Ribavirin when used in combination with these antiviral drugs may be helpful in lowering the chances of relapse.[7]

Received on 11-06-2021
Accepted on 29-11-2021

MATERIALS AND METHODS

This descriptive case series study was carried out at Hayatabad Medical Complex, a tertiary care hospital in Peshawar, Pakistan from 1st October 2017 to 28th February 2019 after approval from IRB. They were given sofosbuvir (400mg) and daclatasvir (60mg) daily, with or without ribavirin, for a period of three to six months. Data regarding the patients suffering from hepatitis C viral infection was collected from the OPD of gastroenterology unit. We excluded those patients who had other liver diseases than hepatitis C as well as patients suffering from HIV and HBV co-infection, pregnancy and patients taking anti-tuberculous treatment. Patients visited the hospital for routine examination every month during their treatment and were advised tests like FBC, LFTs, RFTs, PT, INR and when needed, also abdominal ultrasound. They were asked about any undesirable effect due to medicines. Follow up was done after completing twenty-four weeks of treatment to know the outcome in terms of SVR. The data was entered and analyzed through SPSS-25.

RESULTS

The mean age of the patients were 42.16±11.65 years including 43(43.87%) males and 55(56.12%) females. Fifty-one patients received sofosbuvir and daclatasvir while 47 received sofosbuvir, daclatasvir and ribavirin. Sixty seven patients were given

sofosbuvir and daclatasvir (ribavirin) for 3 months, while 31 subjects received the same medicines for 6 months. End of treatment response (ETR) rate of 93 (94.89%) was observed. Follow up PCR of the patients were done after 6 months of completing 12 to 24 weeks of treatment. SVR rate of 87(88.77%) was achieved, amongst which treatment-naïve patients had SVR rate of 90.27 % (65/72) while SVR rate of 84.61%was observed in treatment-experienced subjects (22/26). Fifty-one patients that received sofosbuvir and daclatasvir achieved SVR rate of 88.23% (45/51) while 47 patients who took sofosbuvir, daclatasvir and ribavirin had a SVR rate of 89.36% (42/47). The SVR rate in patients with 12 weeks treatment (sofosbuvir and daclatasvir ± ribavirin) was 89.55% (60/67), and those patients who received a 24 weeks treatment with the same antiviral drugs achieved SVR rate of 87.09% (27/31). In patients receiving ribavirin containing regimen, the blood haemoglobin level decreased by 0.83 g/dl at the end of therapy, among them 15% patients developed moderate anaemia with an average Hb level of 10.34 g/dl. All patients had raised level of ALT (76.78±52.29 U/L) before commencing treatment but showed marked improvement (36.96±22.19 U/L) at the end of treatment. Majority of patients complained of generalized body aches (24%) and fatigue (21%), with headache (10%) and fever (6%) [Tables 1-2).

End of treatment response rate of 94.89% (93/98) was observed. Out of ninety eight patients, 5 patients were PCR positive (HCV RNA detected), while 93 patients were reported PCR negative (HCV RNA not detected) after 12 or 24 weeks of treatment. Patients were followed up with another PCR test, 24 weeks (6 months) after the date of completion of their treatment to know the treatment outcome in terms of SVR. SVR rate of 88.77% (87/98) was achieved (Fig. 1).

Fifty one patients, who were treated with sofosbuvir and daclatasvir, a sustained virological response rate of 88.23% (45/51) were achieved. Forty seven patients received therapy with sofosbuvir, daclatasvir and ribavirin, and achieved SVR rate of 89.36% (42/47). Patients receiving ribavirin containing regimen resulted in a slightly better viral response (Fig. 2).

Sixty seven patients received 3 months treatment and 31 patients received 6 months treatment (with sofosbuvir-daclatasvir with or without ribavirin), and achieved an SVR rate of 89.55% (60/67) and 87.09% (27/31) respectively (Fig. 3).

Treatment-naïve patients had SVR rate of 90.27 % (65/72) and treatment-experienced patients achieved SVR rate of 84.61 % (22/26). This indicates that newly-treated patients responded well to antiviral therapy (Fig. 4).

Table 1: Basic characteristics of patients (n=98)

Characteristics	**No.**	**%**
Mean age (years)	42.16±11.65	
Gender		
Male	43	43.88
Female	55	56.12
Patients treated with sofosbuvir and daclatasvir	51	52.04
Patients treated with sofosbuvir, daclatasvir and ribavirin	47	47.95
Patients receiving 3 months (12 weeks) treatment	67	68.36
patients receiving 6 months (24 weeks) treatment	31	31.63

Table 2: Frequency of treatment response

End of treatment response rate	94.89% (93/98)
Sustained virological response rate	88.77% (87/98)
SVR rate in treatment naïve patients	90.27% (65/72)
SVR rate in treatment experienced patients	84.61% (22/26)
SVR rate in patients receiving sofosbuvir and daclatasvir	88.23% (45/51)
SVR rate in patients receiving sofosbuvir, daclatasvir and ribavirin	89.36% (42/47)
SVR rate in patients receiving 3 months (12 weeks) treatment	89.55% (60/67)
SVR rate in patients receiving 6 months (24 weeks) treatment	87.09% (27/31)

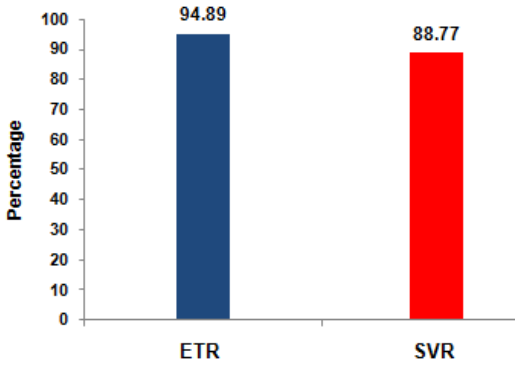

Fig. 1: ETR and SVR rates in 98 patients

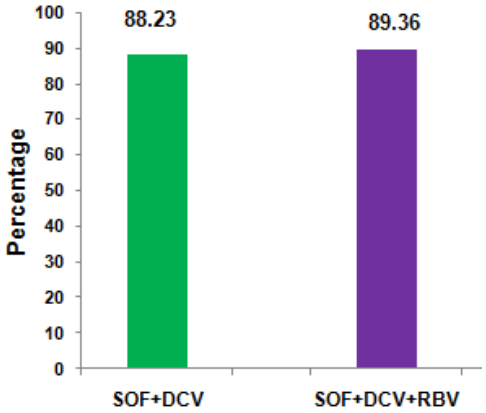

Fig. 2: SVR rate in patients on SOF+DCV versus patients on SOF+DCV+RBV

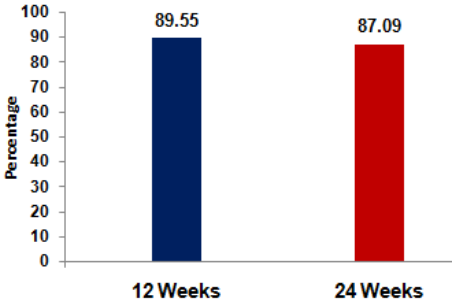

Fig. 3: SVR rate in patients with 12 and 24 weeks treatment

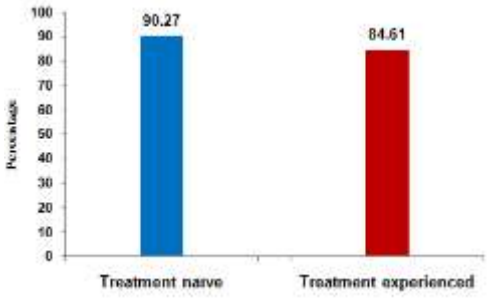

Fig. 4: SVR rate-treatment-naïve and treatment-experienced patients

DISCUSSION

For more than 25 years, pegylated interferon (peg-IFN) along with ribavirin (RBV) was used in patients suffering from chronic

hepatitis C viral infection but this regimen resulted in unfavorable efficacy and more adverse effects.[8] With development of DAAs, the management for HCV infected patients has dramatically changed. Various clinical studies have demonstrated that sofosbuvir-daclatasvir combination, with or without ribavirin are capable of managing chronic hepatitis C patients, particularly those with HCV genotype 1 or 3[9].

The high price of these direct acting antiviral drugs had been a matter of great concern, especially in underdeveloped and developing countries, and so efforts were made to make these drugs available at cheaper rates while at the same time maintaining the efficacy and safety which required scientific evaluation[10].

In this study we used the low-cost sofosbuvir-daclatasvir with or without ribavirin, in chronic HCV patients. SVR rate of 88.77% was observed which was comparable with the international data. In a French study which was carried by Pol et al[11] showed that sustained virological response rate (SVR12) was 92% in HCV genotype 2 infected patients , and 89% in patients with genotype 3, after receiving treatment with sofosbuvir-daclatasvir, with or without ribavirin[12].

In another phase 3 study carried by Christophe Hézode in France, in which 560 patients infected with HCV genotype 3 were enlisted from 4 March to 27 October, 2014. After24 weeks treatment with sofosbuvir and daclatasvir (with or without ribavirin), SVR rate of 89% was achieved.[13,14]

The efficacy of low cost generic of sofosbuvir and daclatasvir has been evaluated through different studies in Pakistan. Umar et al[15], who included patients suffering from chronic hepatitis C viral infection with genotype 3 in his study, reffered from different hospitals of Rawalpindi (Pakistan) during the year 2016-18, showed a sustained virological response rate (SVR12) of 83.33%. These patients received the combined therapy of sofosbuvir-daclatasvir with or without ribavirin. Initially it was thought that adding ribavirin to direct acting antiviral drugs (DAAs) will no longer be required for treating chronic HCV infection but various clinical findings suggest that ribavirin still retains its role. When combined to DAAs, ribavirin improves SVR ratein HCV patients, particularly those with fibrosis liver and treatment experienced.[12]

The low cost generic of sofosbuvir and daclatasvir are safe and effective in treating hepatitis C infection. Availability of these oral antiviral drugs and the new generic of medications used for the management of HCV patients, will be the most effective method in eliminating hepatitis C from the globe by 2030.[14]

Keeping in view the efficacy of sofosbuvir and daclatasvir, it is hoped that these drugs will play a major part in the eradication of hepatitis C viral disease from the developing world.

CONCLUSION

Sofosbuvir plus daclatasvir with or without ribavirin is an effective combination in treating patients suffering from chronic hepatitis C viral infection with high efficacy and fewer side effects.

Conflict of interest: Nil

REFERENCES

1. Sharm D, Surendra K, Munjal YP. API textbook of medicine. 9th ed. Bombay: aypee Brothers, 2012.
2. 2. Pawlotsky JM, Aghemo A, Back D, Dusheiko G, Forns X, Puoti M, Sarrazin C. EASL recommendations on treatment of hepatitis C 2015. J hepatol 2012; 63(1): 199-236.
3. Qureshi H, Bile KM, Jooma R, Alam SE, Afridi HUR. Prevalence of hepatitis B and C viral infections in Pakistan: findings of a national survey appealing for effective prevention and control measures. Eastern Mediterranean Health J 2010; 16: S15-23.
4. Basyte-Bacevice V, Kupcinskas J. Evolution and revolution of hepatitis c management: from non-a, non-b hepatitis toward global elimination. Dig Dis 2020; 38: 137-42.
5. Lam B, Henry L, Younossi Z. Sofosbuvir (Sovaldi) for the treatment of hepatitis C. Expert Rev Clin Pharmacol 2014; 7(5): 555-66.
6. Lim PJ, Gallay PA. Hepatitis C NS5A protein: two drug targets within the same protein with different mechanisms of resistance. J Curr Opinion Virol 2014; 8: 30–37.
7. Tsaturyan S. Patient experience with expanded Basic Benefits Package coverage for treatment of Hepatitis C in Armenia [Thesis]. Turpanjian School of Public Health, American University of Armenia, Yerevan, Armenia, 2002.
8. Gogela NA, Lin MV, Wisocky JL, Chung RT. Enhancing our understanding of current therapies for Hepatitis C virus (HCV). Current HIV/AIDS Reports 2015; 12(1): 68-78.
9. Leroy V, Angus P, Bronowicki JP, et al. Daclatasvir, sofosbuvir, and ribavirin for hepatitis C virus genotype 3 and advanced liver disease: a randomized phase III study (ALLY-3+). J Hepatol 2016; 63(5):1430-41.
10. Gilead Sciences Inc. Chronic hepatitis C treatment expansion: generic manufacturing for developing countries. 2015.
11. Pol S, Bourliere M, Lucier S, De Ledinghen V, Zoulim F, Dorival-Mouly C, Hezode C. Safety and efficacy of the combination daclatasvir-sofosbuvir in HCV genotype 1-mono-infected patients from the French observational cohort ANRS CO22 hepather. J hepatol 2015; 62(Suppl 2): S258.
12. Pol S, Corouge M, Vallet-Pichard A, Daclatasvi-Sofosbuvir combination therapy with or without ribavirin for hepatitis C virus infection: from the clinical trials to real life, J Hepatic Med Evidence Res 2016; 8: 21-6.
13. Hézode C, Lebray P, Boyer N, Larrey D, Filipovics A, Zhao Y, et al. 'Daclatasvir plus sofosbuvir,with or without ribavirin, for hepatitis C virus genotype 3 in a French early access programme., J Liver Int 2017.
14. Hill A, Tahat L, Mohammed MK, Khwairakpam G, Nath S, Freeman J, et al. Bioequivalent pharmacokinetics for generic and originator hepatitis C direct-acting antivirals: Elsevier, 2018.
15. Umar M, Akhter TS, Sadiq J, Saleem S, Khokhar S. Efficacy and safety of generic daclatasvir+ sofosbuvir±ribavirin in treatment of genotype 3 infected hepatitis C patients-a real life experience from Pakistan. *Hepatoma Res 2018; 4.*