Efficacy of Sofosbuvir and Daclatasvir in Achieving the End Treatment Response and Sustained Viral Response in Patients infected with Hepatitis C Virus Genotype 3

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ABSTRACT

Objective: To ascertain the efficacy of sofosbuvir combined with daclatasvir against hepatitis C genotype 3 infection.
Study Design: Prospective longitudinal study.
Place and Duration of Study: Ayub Teaching Hospital, Abbottabad, Pakistan, from Nov 2018 to Jan 2020.
Methodology: About 262 patients were treated during the study. Patients with symptoms associated with liver failure, including ascites, uncontrolled bleeding, encephalopathy and other comorbidities, were excluded from the study. Patients with diagnosed hepatitis C genotype 3 infection were given daclatasvir and sofosbuvir combined with follow-up visits at 12 and 24 weeks of treatment. Primary outcome variables were end treatment response, sustained viral response, non-responders, and relapse rate. In addition, secondary outcomes of patient variables including age, gender, and baseline viral load were observed.
Results: The mean age of patients was 39.8 ± 8.2 years. The twelve-week course of Sofosbuvir and Daclatasvir produced an end treatment response (ETR) of 98.9%, while the sustained virological response was 95.8%. The combination had no adverse effects, and none of the patients reported treatment discontinuation. There were no deaths due to treatment.
Conclusion: The current study indicates that using Sofosbuvir in conjunction with Daclatasvir is an effective drug regime against the Hepatitis C virus, type 3 infection.

Keywords: Daclatasvir, End treatment response, Hepatitis C, Sofosbuvir, Sustained virologic response.

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INTRODUCTION

It is reported that hepatitis C infects over 170,0000 patients globally, and out of those, about ten million patients are suffering in Pakistan.[1] An estimated prevalence of 6% has been noted in Pakistan, with type 3 being the most commonly occurring genotype. In low socioeconomic countries like Pakistan, there are usually poor health-care standards and insufficient implementation of proper protocols in health-care settings.[2] Reuse of syringes and needles, sharing of needles among IV drug abusers, local barbers who use unsterilized blades for shaving, blood transfusion, improper disinfection of instruments used in surgical procedures are the main transmitting factors for HCV in Pakistan.[3] There are 11 different genotypes of HCV, of which type 3a is the most prevalent in Pakistan, with a reported frequency between 75% to 90% cases.[4]

Hepatitis C virus type 3 has been linked with cirrhosis, steatosis, and liver cancer, and the complication rates are higher in these patients compared to other viral genotypes.[5-6]

There have been many recent breakthroughs in novel treatment regimens effective against HCV infection. With the discovery of interferon-alpha, which can be used alone or in combination with pegylated interferon-alpha and Ribavirin, the pharmacological ability to attain sustained virologic response (SVR) has substantially enhanced. Nevertheless, due to serious adverse effects of these drugs, patients become non-compliant and even withdraw from treatment in more than 10 to 15 percent of the cases.[7-8]

Recently, novel antiviral therapies have been endorsed for treating HCV type 3 infection, including a potent drug called Sofosbuvir.[9] Sofosbuvir is a pangenotypic nonstructural protein [NS]5B inhibitor combined with Ribavirin or pegylated IFN (Peg-IFN) plus Ribavirin is very effective against HCV genotype.[3] Daclatasvir, another potent pangenotypic NS5A inhibitor, has also shown promising results against the virus when used adjunctively with sofosbuvir and Ribavirin.[10]

Nevertheless, many side effects are associated with Ribavirin; thus, patients often drop out and

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abandon the treatment.[7-8] In a developing country, the affordability of antiviral drugs is also a major concern. Therefore, it becomes crucial to explore more effective treatment regimens against HCV infection, preferably with shorter therapy regimes and without the need to add Ribavirin or Peg-IFN. In the present study, we evaluated the efficacy of the combination of SOF and DCV for treating hepatitis C virus genotype 3 infection in our population.

METHODOLOGY

This study was conducted from November 2018 to January 2020 at the Department of Gastroenterology and Hepatology, Ayub Teaching Hospital, Abbottabad. Participants were selected via a non-randomized convenience sampling technique. The sample size of 262 was calculated using select statistics software, keeping the prevalence of Hepatitis C, type 3 as 58.16% 11, with a confidence level of 95% and a margin of error of 5.97.

Inclusion Criteria: All patients diagnosed with chronic hepatitis C virus, genotype 3 with a positive PCR were inducted into the study.

Exclusion Criteria: Patients with symptoms associated with liver failure, including ascites, uncontrolled bleeding, encephalopathy and other comorbidities, were excluded from the study. In addition, patients who were refractory to previous treatment therapy with NS5A inhibitors or had a history of discontinuation of treatment with Sofosbuvir and Daclatasvir before attaining the sustained viral response were also excluded.

Ethical approval was procured from the Institutional Review Board Committee of Ayub Teaching Hospital (IRB/Gastro/876), Abbottabad and informed written consent was secured from all individuals before the initiation of the treatment.

All patients diagnosed with HCV genotype 3 were treated with 400 milligrams of sofosbuvir and 60 milligrams of daclatasvir daily for twelve weeks, with follow-up visits at 12 and 24 weeks of treatment. All patients were asked to record daily medicine/dosing intake and mention the pills missed (if any). Patient compliance with study treatment was assessed at each follow-up visit. Before starting the study, HCV-RNA titres were determined, and then again, titres were determined at 12 weeks of treatment and 24 weeks post-treatment using the COBAS TaqMan HCV test, keeping a lower limit of quantitation (LLOQ) of 25 IU/mL. In addition, ETR at 12 weeks of treatment was determined for all patients.

ETR was denoted as the undetectable hepatitis C virus in the blood after twelve weeks of therapy. Patients who had an HCV-RNA PCR positive were labelled as non-responders. Patients who tested negative PCR (i.e., who achieved an ETR) after completing the treatment were followed up for 24 weeks to see if they achieved a sustained viral response (SVR) or relapsed.

Sustained virologic response (SVR) was described as undetectable levels of HCV-RNA twenty-four weeks after completion of pharmacological therapy with Daclatasvir (DCV) plus Sofosbuvir (SOF). Patients who were followed up till 24 weeks were either classified as HCV-RNA PCR positive or negative or lost to follow-up.

SVR-12 was taken as the undetectable levels of viral RNA in the blood 12 weeks post-therapy with Daclatasvir (DCV) plus Sofosbuvir (SOF). This was done to document the relapse rate in our population. Relapse is said to have occurred when HCV-RNA is detectable in the blood after the completion of antiviral therapy. Therefore, it is most likely to occur within 12 weeks after treatment.

Primary outcome variables were the rate of endtreatment-response, sustained virological response, the frequency of non-responders, and the relapse rate. In addition, secondary outcomes of patient variables including age, gender, body mass index (BMI), and baseline viral load were observed.

The study data was analyzed using the Statistical Package for Social Sciences (SPSS) version 25. The continuous variables, including the age and body mass index, were presented as mean plus SD. Categorical variables were presented as frequency and percentages, including the ETR, SVR-12, SVR-24, relapse rate, etc.

RESULTS

A total of 262 participants were enrolled in the study. A mean age of 39.8 ± 8.2 years was observed. In the present study, more than half of the population, i.e. 163 (60.7%), were women, while only about 40 percent were men. The majority, i.e. 111 (42.7%) participants, belonged to the Hindko ethnic group (Table-I).

In the present study, 259 (98.9%) out of 262 patients achieved the end treatment response (ETR) as indicated by the undetectable viral RNA load on the polymerase chain reaction test at 12 weeks of treatment. After 12 weeks of treatment. 248 (95.8%) patients were negative for viral load. In the study, only three patients did not respond to the antiviral therapy

and eleven patients suffered from a relapse within 12 weeks of treatment. The sustained viral response at 24 weeks follow-up was observed in 96.8% of patients (Table-II).

Table-I: Clinical and demographic profile (n=262).

Parameter	n (%)
Mean Age ± SD	39.8 ± 8.2 years
Average body mass index	25.3 ± 13.6 kg/m^2
Gender	
Male	163 (60.7%)
Female	99 (39.3%)
Marital Status	
Unmarried	80 (30.6%)
Married	182 (69.4%)
Ethnicity	
Hindko (Hazara)	111 (42.7%)
Pushtoon	46 (17.8%)
Afghani (refugees)	39 (14.9%)
Others; Kohistan, Gilgiti and Kashmiris	66 (24.9%)
HCV-RNA level in IU/mL	
<800,000	75 (28.6%)
≥800,000	187 (71.4%)

Table-II: Virological Response of patients (n=262).

Parameter	n (%)
End Treatment Response (ETR)	
HCV-RNA positive (non-responders)	3 (1.1%)
HCV-RNA negative	259 (98.9 %)
Sustained Viral Response (12 weeks)	
HCV-RNA positive	11 (4.2%)
HCV-RNA negative	248 (95.8%)
Sustained Viral Response (24 weeks)	
HCV-RNA positive	8 (3.2%)
HCV-RNA negative	240 (96.8%)
Non-responders (%)	3 (1.1%)
Relapse rate within 12 weeks post antiviral therapy (%)	11 (4.2%)
Relapse rate within 24 weeks post antiviral therapy (%)	8 (3.2%)

DISCUSSION

In the present study, the twelve-week treatment with Sofosbuvir and Daclatasvir produced an end treatment response (ETR) of 98.9% against HCV genotype 3 infection with only three non-responders. The SVR at twelve weeks (SVR-12) was 95.8% in our study. A relapse rate of 4.2% was noted within 12 weeks after the completion of antiviral therapy, while a relapse rate of 3.2% was observed following 24 weeks of antiviral therapy. 1.1% of our study population was non-responsive to the DCV and SOF regimen. SVR at 24 weeks posts antiviral therapy was 96.8%. The adjunctive therapy of Sofosbuvir and Daclatasvir was well tolerated, with insignificant side effects. No deaths or treatment discontinuation due to adverse effects were observed.

Our findings align with earlier data from a randomized control trial evaluating the efficacy and tolerability of Daclatasvir prescribed in combination with Sofosbuvir, with or without additional Ribavirin, in patients with HCV genotype 3 infections.[12-13] Broadly, our findings indicate that in patients with HCV genotype 3 infection without severe liver disease or other comorbidities, a 12-week treatment regimen with DCV plus SOF is highly effective compared with the 24-week regimens containing Ribavirin.

In a study by Gane *et al,* it was observed that the 12-week treatment regimen with a combination of Ledipasvir or Sofosbuvir along with Ribavirin provided SVR-12 rates of 89% in HCV genotype 3 patients and no cirrhosis. However, the SVR-12 rate of 77% was observed in patients with cirrhotic liver.[14] The present study observed a much better SVR-12 rate of 95.8% with a combination of DSV and SOF without adding Ribavirin. Nevertheless, we did not analyze sub-categories of patients, which is a limitation of the current study. Further studies should evaluate the sustained virologic response of the regimen in sub-categories of patients, i.e. patients with cirrhotic liver, etc. One such study by Ho *et al*. evaluated the pharmacokinetics of sofosbuvir when given adjunctively with Ribavirin among cirrhotic patients and multiple comorbidities. He evaluated that 12-week administration of sofosbuvir along with Ribavirin provided an SVR-12 weeks after completion of antiviral therapy of 80% in hepatitis C virus patients with associated liver damage, cirrhosis, and/or other comorbid conditions.[15]

The combination of Sofosbuvir plus Daclatasvir has shown a promising safety and efficacy profile. In addition, we reported no significant side effects of the drugs, and no deaths or treatment discontinuation associated with adverse events from the antiviral therapy were observed in the study. In contrast, previously published studies have reported the incidence of hemolytic anaemia in patients treated with the dual therapy of SOF plus Ribavirin.[16-18] In conclusion, our study reported an ETR of 98.9%, an SVR-12 of 95.8%, and an SVR-24 of 96.8%, with the dual pharmacotherapy of DSV and SOF.

CONCLUSION

The present study indicates that the adjunctive pharmacotherapy of Sofosbuvir plus Daclatasvir is an effective drug regime against the diagnosed infection of Hepatitis C virus (type 3) in the study population. Further large-scale,

diversified studies should focus on exploring the risk factors associated with treatment failures and reduced sustained virologic response rate.

Conflict of Interest: None.

Authors' Contribution

ZU: Concept/valization, revision, SZK: Study design, data acquisition, HL: Data acquisition, entry, HK: Drafting of paper, RH: Critical revision, MA: Statistical analysis.

REFERENCES

1. Blach S, Zeuzem S, Manns M, Altraif I, Duberg AS, Muljono DH, et al. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: A modelling study. Lancet Gastroenterol Hepatol 2017; 2(3): 161-76. doi: 10.1016/S2468-1253(16)30181-9.
2. Al Kanaani Z, Mahmud S, Kouyoumjian SP, Abu-Raddad LJ. The epidemiology of hepatitis C virus in Pakistan: Systematic review and meta-analyses. R Soc Open Sci 2018; 5(4): 180257. doi: 10.1098/rsos.180257.
3. Waheed Y, Shafi T, Safi SZ, Qadri I. Hepatitis C virus in Pakistan: a systematic review of prevalence, genotypes and risk factors. World J Gastroenterol 2009; 15(45): 5647-5653. doi: 10.3748/wjg.15.5647.
4. Hamid S, Umar M, Alam A, Siddiqui A, Qureshi H, Butt J. PSG consensus statement on management of hepatitis C virus infection--2003. JPMA. J Pak Med Assoc 2004; 54(3): 146-150.
5. Nkontchou G, Ziol M, Aout M, Lhabadie M, Baazia Y, Mahmoudi A, et al. HCV genotype 3 is associated with a higher hepatocellular carcinoma incidence in patients with ongoing viral C cirrhosis. J Viral Hepat 2011; 18(10): e516-e522. doi: 10.1111/j.1365-2893.2011.01441.x.
6. Kanwal F, Kramer JR, Ilyas J, Duan Z, El-Serag HB. HCV genotype 3 is associated with an increased risk of cirrhosis and hepatocellular cancer in a national sample of US Veterans with HCV. Hepatol 2014; 60(1): 98-105. doi: 10.1002/hep.27095.
7. Hézode C, Forestier N, Dusheiko G, Ferenci P, Pol S, Goeser T, et al. Telaprevir and peginterferon with or without ribavirin for chronic HCV infection. N Engl Jo Med 2009; 360(18): 1839-1850. doi: 10.1056/NEJMoa0807650.
8. Zeuzem S, Berg T, Moeller B, Hinrichsen H, Mauss S, Wedemeyer H, et al. Expert opinion on the treatment of patients with chronic hepatitis C. J Viral Hepat 2009; 16(2): 75-90. doi: 10.1111/j.1365-2893.2008.01012.x.
9. Chahal HS, Marseille EA, Tice JA, Pearson SD, Ollendorf DA, Fox RK, et al. Cost-effectiveness of early treatment of hepatitis C virus genotype 1 by stage of liver fibrosis in a US treatment-naive population. JAMA intern med 2016; 176(1): 65-73. doi: 10.1001/jamainternmed
10. Gandhi Y, Eley T, Fura A, Li W, Bertz RJ, Garimella T. Daclatasvir: A review of preclinical and clinical pharmacokinetics. Clin Pharmacokinet 2018; 57(8): 911-928. doi: 10.1007/s40262-017-0624-3.
11. Haqqi A, Munir R, Khalid M, Khurram M, Zaid M, Ali M, et al. Prevalence of hepatitis C virus genotypes in Pakistan: current scenario and review of literature. Viral Immunol 2019; 32(9): 402-413. doi: 10.1089/vim.2019.0058
12. Zeuzem S, Dusheiko GM, Salupere R, Mangia A, Flisiak R, Hyland RH, et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. N Engl J Med 2014; 370(21): 1993-2001. doi: 10.1056/NEJMoa1316145
13. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson I, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med 2014; 370(3): 211-221. doi: 10.1056/NEJMoa1306218.
14. Gane E, Hyland R, An D, Svarovskaia E, Pang P, Symonds W, et al. High Efficacy of LDV/SOF Regimens for 12 Weeks for Patients with HCV Genotype 3 or 6 Infection: LB-11. Hepatol 2014; 60(6); 1-5.
15. Ho SB, Monto A, Peyton A, Kaplan DE, Byrne S, Moon S, et al. Efficacy of sofosbuvir plus ribavirin in veterans with hepatitis C virus genotype 2 infection, compensated cirrhosis, and multiple comorbidities. Clin Gastroenterol Hepatol 2017; 15(2): 282-288. doi: 10.1016/j.cgh.
16. Hamza I, Eid Y, El-Sayed M, Marzaban R, Abdul-Kareem S. Thyroid dysfunction in chronic hepatitis C patients treated with the combined pegylated interferon-ribavirin therapy. J Interferon Cytokine Res 2016; 36(9): 527-533. doi: 10.1089/jir.2016.0007.
17. Jacobson IM, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. N Engl J Med 2013; 368(20): 1867-1877. doi: 10.1056/NEJMoa1214854.
18. Tong MJ, Chang PW, Huynh TT, Rosinski AA, Tong LT. Adverse events associated with ribavirin in sofosbuvir-based therapies for patients with chronic hepatitis C: A community practice experience. J Dig Dis 2016; 17(2): 113-121. doi: 10.1111/1751-2980