DOI: https://doi.org/10.53350/pjmhs22165240

ORIGINAL ARTICLE

Efficacy of Daclatasvir with Sofosbuvir for Treating Chronic Hepatitis C Genotype 3

FAHAD AMAN KHAN[1], MUKHTAR AHMAD[2], IMRAN KHAN[3], ANIQA ANSER TUFAIL KHAN[4], MUHAMMAD KASHIF[5], TASHIA MALIK[6]
[1,2,3]Assistant Professor, Allama Iqbal Medical College/Jinnah Hospital Lahore
[4]Assistant Professor, Azra Naheed Medical College, Lahore
[5]Assistant Professor, University College of Medicine and Dentistry, University of Lahore, Lahore
[6]Senior Registrar, Jinnah Hospital Lahore
Correspondence to: Dr Fahad Aman Khan, Cell: 03334344400, Email: dr.fahadamankhan@gmail.com

ABSTRACT

Objective: To determine efficacy of Daclatasvir with sofosbuvir in treating patients of chronic hepatitis C genotype 3.
Study Design: Interventional case-series study
Place and Duration of Study: Hepatitis Clinic, Medical Unit–II, Jinnah Hospital, Lahore from January 2019 to June 2019.
Methodology: One hundred and thirty five patients of chronic hepatitis C Genotype 3 were enrolled. All patients were givendaclatasvir60mg and sofosbuvir 400mg once-daily for 12 weeks. HCV-RNA-PCR was done at end of 12 weeks of treatment (ETR) and 12 weeks after end of treatment (SVR).
Results: The mean age of the patients was 49.8 ±2.3 years. There were 57.7% males while 42.2% females with 22.2% frequency of cirrhosis in them.The mean value of AST and ALT was calculated as 57.07 ± 48.69 and 51.02 ± 44.17 IU/ml respectively in hepatitis C patients having genotype 3.The treatment follow up showed that on reassessing the hepatitis C status through quantitative analysis of genotype 3 through PCR it was seen that 91.1% patients reached SVR with no viral detection in them.
Conclusion: Daclatasvir in combination to sofosbuvir is an efficient way of treating hepatitis C patients suffering from genotype 3.
Keywords: Viral load, Sofosbuvir, HCV, Genotype 3

INTRODUCTION

Hepatitis C is a small single stranded RNA based virus belonging to the hepacivirus family and genus Flaviviridae. It has seven main genotypes (1-7). Each genotypes further consists of various sub genotypes.[1] Regionally genotype 1 is predominantly observed in Europe and America.[2] While genotype 4 is highly observed in Middle East population.[3] Japan and China are also prevalent in genotype 1. In Pakistan the main genotype seen is genotype 3 with an occurrence rate of 67-87%.[2,3] Genotype 3 has been causing mega viral load on hepatic population with a major reason of causing cirrhosis in them I addition to stenosis and hepatocellular carcinoma.[4] Intravenous injections and blood transfusion are the main reasons of hepatitis C transmission. Clinician targets in treating this virus prior to development of complications and prognosis of hepatic disease.[5]

Daclatasviris a inhibitor of hepatic virus with a NS5 A inhibition complex. NS5A is basically a viral- protein which causes viral replication as well as its assembly. An oral dosage of this drug can inhibit further replication of the virus with recommended doses as 60mg per day.There has not been a severe side effects reporting in regards to the daclatasvir except diarrhea, nausea, fatigue and headaches.[6]

Another drug namely sofosbuvir is an inhibitor of NS5B complex. It inhibits this protein which is involved in the hepatic virus synthesis. This drug is recommended in 400mg per day dosage with a reported efficient tolerance.[7]The reported SVR rate with these drugs is 89-92% in various studies in cases of genotype 3 and genotype 2.[8,9]

End stage liver disease, cirrhosis and hepatocellular carcinoma from chronic hepatitis C Genotype 3 represents heavy burden in the hospitals of Pakistan leading to multiple outdoor visits, in-hospital stay and lot of economic burden on health system. Above all it is not clear that factors like geographical variation, race and ethnic background affects the efficacy of Daclatasvir with Sofosbuvir in treating chronic hepatitis C genotype 3.No data has been published yet on Daclatasvir with Sofosbuvir regarding local population. The rationale of this study is to establish the role of Daclatasvir with Sofosbuvir for the treatment of hepatitis C Genotype 3 in local population so that it may be used to effectively reduce the morbidity and mortality and hepatitis C related overall disease burden in the society.

MATERIAL AND METHODS

This interventional case series study was conducted in the Hepatitis Clinic, Medical Unit - II, Jinnah Hospital Lahore from January 2019 to June 2019 and 135 patients were enrolled. Patients of chronic hepatitis C Genotype 3, both sex and aged 18-80 years were included. Patients with other chronic diseases e.g. chronic kidney disease, allergic to either daclatasvir or sofosbuvir, autoimmune disorders e.g. SLE, RA and co-infected with HBV and/or HIV were excluded. The sample size was estimated after keeping 95% CI and 7% margin of error. Patients were categorized for having compensated-cirrhosis on the basis of the clinical evaluated data, Child-Pugh scoring and radiological abdominal-imaging. Demographic information e.g. age, sex and address were obtained after taking informed consent from the patient. All patients were givendaclatasvir-60mg and sofosbuvir 400mg once-daily for 12 weeks. HCV-RNA-PCR was done at end of 12 weeks of treatment (ETR) and 12 weeks after end of treatment (SVR).The outcomes were recorded in predesigned proforma which included measurement of quantitative PCR HCV viral load within a detectable range as 12IU/ml. The primary-endpoint for the treatment was achievement of SVR which was defined as undetectable viral-load at the end of the 12 weeks. The data was entered and analyzed through SPSS-20 version 25.0. The Chi square test was applied and p value <0.05 was considered as significant.

RESULTS

The mean age of the patients was 49.8±2.3 years with the duration of hepatitis disease was 5.1±3.7 years. There were 14 patients who were undergoing dialysis and had a mean dialysis period as 4.32±2.59 years. There were 57.7% males while 42.2% females with 22.2% frequency of cirrhosis in them (Table 1).

Table 1: Clinical and Demographic patient characteristics (n=135)

Variables	
Age (Years)	49.8 ±2.3
Hepatitis duration (years)	5.1 ± 3.7
Dialysis duration in 14 patients	4.32 ± 2.59
HCV-RNA-PCR (log 10 IU/ml)	5.88 ± 6.0
Gender	
Male	78 (57.7%)
Female	57 (42.2%)
Cirrhosis	30 (22.2%)

The mean value of AST and ALT was calculated as 57.07 ± 48.69 and 51.02 ± 44.17 IU/ml respectively in hepatitis C patients having genotype 3. The majority of the patients were anemic with a mean hemoglobulin level as 10.54 ± 1.62 (Table 2).

The treatment follow up showed that on reassessing the hepatitis C status through quantitative analysis of genotype 3 through PCR it was seen that 91.1% patients reached SVR with no detectable viral while 82.9% were ETR with no virus detection and only 16.3% having detectable viral load (Table 3).

Table 2: Biochemical characteristics of hepatitis C genotype 3 patients (n=135)

Variables	Mean±SD
AST (U/L)	57.07 ± 48.69
ALT (U/L)	51.02 ± 44.17
HB (g/dl)	10.54 ± 1.62
WBC × 10^3/mm3	6.25 ± 1.94
Plt×10^3/mm3	163.31 ± 65.44

Table 3: Follow-up of patients (n=135)

Variable	Not Detectable	Detectable	P value
4th Week (RVR)	101 (74.8%)	34 (25.1%)	0.031
8th Week	112 (82.9%)	22 (16.3%)	0.045
12th Week (ETR)	112 (82.9%)	22 (16.3%)	0.045
24th Week (SVR)	123 (91.1%)	12 (8.8%)	0.001

The daclatasvir in combination to sofosbuvir seemed to be an efficient treatment method as only 7.4% cases had detectable viral load at the start of the treatment while it was achieved to its maximum health outcome by week 24 (Fig. 1).

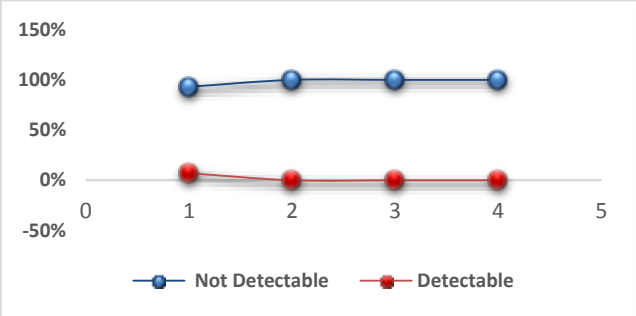

Fig. 1: Viral load detection curve until 24 weeks (SVR)

DISCUSSION

Hepatitis C is a prevalent disease of developing countries with a 6.8% endemic rate whiles an increase upto forty percent within recent years [10]. The present study was designed to assess the efficacy of the Daclatasvir in combination to Sofosbuvir in Chronic Hepatitis C Genotype 3 patient treatment. Studies have elaborated that SOF is one of the most advanced and potent way of treatment for hepatitis C patients, however the dose should not be compromised for better treatment result. The Daclatasvir in combination to Sofosbuvir has also been found efficient choice in patients suffering from genotype 1 and 2 other than genotype 3[11]. Patients suffering from chronic kidney diseases are however still under consideration for usage of this treatment and have not been substantially evaluated through scientific literature in countries like Pakistan.[10,12-14]

Various literatures[15,16] have supported that SVR was 89.4% non-detectable viral load in treatment based on SOF. This is similar to the results of the current study which showed a decrease in detectable viral load and not detected cases were 91.1% at 24th week of their treatment. In the present study cases of genotype 3 were only assess however the literature also supports the fact that within the patients who undergotreatment with SOF there is majority of the cases suffering from HCV genotype 3 while only few cases of genotype 1 and genotype 2 are reported.[10]

An Indian study also reported the fact that dialysis patients having hepatitis C are majority with genotype 3 followed by genotype 1. Patients undergoing hemodialysis are treated with various drug regime and dosage[17-18]. Many are treated with SOF daily dosage in addition to ribavirin.[19]

In another study two various SOF dosageregimes was compared for identifying best suited dose for hepatitis C patients. There study results showed that daily SOF was best recommended dose schedule than three times weekly in the other group. The results showed no relapse cases in the daily Daclatasvir in combination to Sofosbuvir treatment.[20]

CONCLUSION

Daclatasvir in combination to sofosbuvir is an efficient way of treating hepatitis C patients suffering from genotype 3 however mega studies are required to prove these facts.

REFERENCES

1. Negro F, Alberti A. The global health burden of hepatitis C virus infection. Liver Int2011;31(Suppl 2):1-3.
2. Shah HA, Jafri W, Malik I, et al. Hepatitis C virus genotypes and chronic liver disease in Pakistan. J GastroenterolHepatol 1997;12:758-61.
3. Idrees M, Riazuddin S. Frequency distribution of hepatits C virus genotype in different geographical regions of Pakistan and their possible routes of transmission. BMC Infec Dis 2008;8:69
4. Larsen C, Bousquet V, Delarocque-Astagneau E, et al. HCV Surveillance Steering Committee Hepatitis C virus genotype 3 and the risk of severe liver disease in a large population of drug users in France. J Med Virol2010;82:1647-54.
5. McCombs J, Matsuda T, Tonnu-Mihara I, et al. The risk of long-term morbidity and mortality in patients with chronic hepatitis C: results from an analysis of data from a department of veterans affairs clinical registry. JAMA Intern Med 2014;174:204-12.
6. Wang C, Valera L, Jia L, Kirk MJ, Gao M, Fridell RA. In vitro activity of daclatasvir on hepatitis C virus genotype 3 NS5A. Antimicrob Agents Chemother2013;57:611-3.
7. Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. N Engl J Med 2013;368:1878-87.
8. Nelson DR, Cooper JN, Lalezari JP et al. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. J Hepatol2015;61(4):1127-35.
9. Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. N Engl J Med 2014;370(3):211-21.
10. Umer M, Iqbal M. Hepatitis C virus prevalence and genotype distribution in Pakistan: comprehensive review of recent data. World J Gastroenterol 2016; 22(4):1684.
11. Sulkowski MS, Jacobson IM, Nelson DR. Daclatasvir plus sofosbuvir for HCV infection. N Engl J Med 2014; 370(16):1560.
12. Butt AA, Ren Y, Puenpatom A, Arduino JM, Kumar R, Abou-Samra AB. HCV treatment initiation in persons with chronic kidney disease in the directly acting antiviral agents era: results from ERCHIVES. Liver Int 2018;38(8):1411-7.
13. Suda G, Furusyo N, Toyoda H, Kawakami Y, Ikeda H, Suzuki M, et al. Daclatasvir and asunaprevir inhemodialysis patients with hepatitis C virus infection: a nationwideretrospective study in Japan. J Gastroenterol 2018;53(1):119-28.
14. Atsukawa M, Tsubota A, Toyoda H, Takaguchi K, Nakamuta M, Watanabe T, et al. The efficacy andsafety of glecaprevir plus pibrentasvir in 141 patients with severe renalimpairment: a prospective, multicenter study. Aliment PharmacolTher 2019;49(9):1230-41.
15. Atsukawa M, Tsubota A, Koushima Y, Ikegami T, Watanabe K, Shimada N, et al. Efficacy and safety of ombitasvir/ paritaprevir/ritonavir in dialysis patients with genotype 1b chronic hepatitis C. Hepatol Res 2017;47(13):1429-37.
16. Li T, Qu Y, Guo Y, Wang Y, Wang L. Efficacy and safety of direct-acting antivirals-based antiviral therapies for hepatitis C virus patients with stage 4- 5 chronic kidney disease: a meta-analysis. Liver Int 2017;37(7):974-81.
17. Agarwal SK, Bagchi S, Yadav RK. Hemodialysis patients treated for hepatitis C using a sofosbuvir-based regimen. Kidney Int Rep 2017;2(5):831-5.
18. Gane EJ, Robson RA, Bonacini M, Maliakkal B, Liu L, Sajwani K, et al. Safety, Anti-viral Efficacy and Pharmacokinetics (pk) of Sofosbuvir (sof) in patients with severe renal impairment: Hepatology 2014;60:667A.
19. Desnoyer A, Pospai D, Lê MP, Gervais A, Heurgué-Berlot A, Laradi A, et al. Pharmacokinetics, safety and efficacy of a full dose sofosbuvir-based regimen given daily in hemodialysis patients with chronic hepatitis C. J Hepatol 2016;65(1):40-7.
20. Ram BK, Frank C, Adam P, Cynthia L, Maria H, Lennox J, et al. Safety, efficacy and tolerability of half-dose sofosbuvir plus simeprevir in treatment of hepatitis C in patients with end stage renal disease. J Hepatol 2015;63(3):763