Open Access

Original Article

Outcomes of the Use of Direct-Acting Antiviral Therapy in Patients of Chronic Hepatitis-C of Genotype 3a

Sarmad Zahoor, Sikander Abdullah, Muhammad Ahmed Saifullah, Saroosh Zahoor*, Khan Amer, Shoaib Ali**

Mayo Hospital Lahore, Pakistan, *University of Management & Technology, Lahore Pakistan, **Rahbar Medical and Dental College, Lahore Pakistan

ABSTRACT

Objective: To measure the outcomes of direct acting Antiviral therapy in terms of frequency of Hepatocellular carcinoma after its use of in HCV patients infected with 3a genotype and to analyze the efficacy of double and triple regimen in HCV patients of Child Pugh's class A and B respectively.

Study Design: Quasi- experimental study.

Place and Duration of Study: Mayo Hospital, Lahore Pakistan, from May to Dec 2019.

Methodology: After applying inclusion and exclusion criteria 262 patients of 3a genotype were awarded as Child Pugh's Class A and B and were treated with double and triple regimen for 12 and 24 weeks respectively. They were followed up with Ultrasound Abdomen every month and PCR Quantitative was done for evaluating Sustained Virological Response after 3 months of completing treatment.

Results: Out of 262 patients, 141(53.8%) were male and 121(46.2%) were female. 243(92.7%) patients achieved Sustained Virological Response. 9(3.4%) developed Hepatocellular carcinoma of which 8 were on triple regimen and 1 on double regimen.

Conclusion: direct Acting Antivirals are effective in achieving Sustained Virological Response but pose a greater risk for Hepatocellular carcinoma. So, they should be used with caution and serial monitoring.

Keywords: Declatasvir, Hepatitis-C, Hepatocellular Carcinoma, Sofosbuvir, Sustained virological response.

How to Cite This Article: *Zahoor S, Abdullah S, Saifullah MA, Zahoor S, Amer K, Ali S. Outcomes of the Use of Direct-Acting Antiviral Therapy in Patients of Chronic Hepatitis-C of Genotype 3a. Pak Armed Forces Med J 2023; 73(Suppl-1): S69-72. DOI: https://doi.org/10.51253/pafmj.v73iSUPPL-1.5798*

INTRODUCTION

Hepato-cellular Carcinoma (HCC) is one of the commonest primary malignancies of liver and has proven to be a leading cause of cancer related mortality globally.[1] Among etiologies, HBV and HCV are the most common causes along with alcohol abuse (found to put synergistic effect with HBV and HCV) and nonalcoholic fatty liver disease (NAFLD).[2] Among these causes, HCV remains a major contributor to HCC (1-8% of contracted cases) since its percentage is increasing over the years.[3] After failure of acyclovir and Ribavirin to lower viral load in HCV, Interferon was introduced as a treatment for HCV. INF with Ribavirin showed an SVR of 24% after treatment for 24 weeks which improved to 54% after pegylation of INF for 48 weeks in western studies.[4] However it was shown that INF based regimen not only improved fibrosis and cirrhosis of Liver after achieving SVR but also became a lesser likely cause of HCC.[5]

SVR was further improved to 92% (for 3a genotype) with introduction of direct acting antiviral (Simepravir, Declatasvir, Sofosbuvir) which were effective and easily tolerable with lesser side effects. However SVR was variable for different genotypes.[6] On the other hand with the use of DAA in HCV patients; occurrence of HCC was found higher.[7,8] It was found to be 3.2% and 7.4% within 6 months and 12 months respectively.[5,9] Since HCC is a life threatening condition it needs to be addressed vigilantly. Data suggestive of HCC occurrence following DAA is deficient and no local study is available in Pakistan according to our knowledge. Here we have studied prevalence of HCC after use of DAA in HCV patients in addition to studying its efficacy in terms of achieving SVR.

Aims and Objectives

To measure the outcomes of DAA in terms of frequency of HCC after use of DAA in HCV patients infected with 3a genotype and toanalyzeefficacy of double and triple regimen in HCV patients of Child Pugh's class A and B respectively.

MEHODOLOGY

The quasi-experimental study was conducted at Mayo Hospital, Lahore from May to December 2019. Ethical Review certificate (ERC) Number was DLS-BCC-2018-01-01. Patients were selec-ted through non-probability convenience sampling technique. A sample size of 262 was calculated with 95% confidence interval

Correspondence: Dr Sarmad Zahoor, Department of Medical, Mayo Hospital Lahore, Pakistan

Received: 09 Mar 2020; revision received: 01 Feb 2021; accepted: 09-Feb-2021

and 5% margin of Error and expected prevalence of HCC after standard treatment as 12.8%.[10]

Inclusion Criteria: Patients of either gender, aged between 18 and 70 years who contracted with genotype 3a with no lesion on USG belonging to Child Pugh class A and B and not known to have any psychiatric illness were included in this study.

Exclusion Criteria: Any patient belonging to Child Pugh's class C were excluded from study. Pregnant, underweight, psychiatric pati-ents and those showing any focal lesion on USG or having co-infection with HBV were also excluded.

CBC, LFTs,RFTs, PT, INR and Ultrasound (USG) Abdomen were performed along with PCR Quantitative and genotyping for HCV at the start of treatment. A detailed history pertaining to risk factors of hepatitis C and HCC was taken. Patients were classified according to Child Pugh'sScore. The patient belonging to Child Pugh's Class-A were treated with double regimen (Sofosbuvir 400mg once daily and Ribavirin 400mg three times a day) for 12 weeks and those of Class-B were given triple regimen (includes Declatasvir 60mg along with double regimen once in a day) for 24 weeks.

Patients were followed up every month with CBC and USG Abdomen. PCR Quantitative was repeated at the end of treatment to analyze end of treatment response. PCR was again repeated for checking sustained viral response three months after completion of treatment along with USG Abdomen. Those patients which proved to have HCC on USG at any stage of treatment or after the treatment were followed up with their alpha-fetoprotein levels. All the data was collected with the help of a performa that included consent of the patient, his history and follow up details for future. Data collected from the patients was analyzed in SPSS.[20] All baseline charecters and variables in history were calculated as Mean and standard deviations for quantitative variables and as percentags for frequencies of qualitative variables. Univariate comparison for binary variables was performed with Chi-Square. (a *p*-value of less than 0.05 was considered significant).

RESULTS:

Of 262 enrolled patients, 141(53.8%) were male and 121(46.2%) were female. 92.7%(243) patients showed SVR describing efficacy of DAA. The patients who developed HCC after DAA were 9(3.4%) out of which 5 were male and 4 were female. Only one patient of compensated cirrhosis belonging to class A on double regimen developed HCC. Rests were on triple regimen. Mean of age, AST, ALT and creatinine was 52.78± 5.73, 72.2±46.32, 75.08±44.99 and 0.8±0.2 respectively. Relative distribution of all variables is shown in following Table-I.

Table-I: Frequency distribution comparision between the Gender (n=262)

Frequency Distribution of all Variables	Average/ Total	Male	Female
Age (years)	52.78±5.73	51.53±5.53	54.23±5.64
Sex	262	141(53.8%)	121(46.2%)
Child-Pugh Class-A	186(71.%)	105(56.45%)	81(43.55%)
Child-Pugh Class-B	76(29%)	36(47.37%)	40(52.63%)
Sustained Virological Response Achieved	243(92.7%)	130(53.5%)	113(46.5%)
Hepatocellular Carcinoma	9(3.4%)	5(55.6%)	4(44.4%)
Sustained Virological Response not achieved	19(7.3%)	11(57.9%)	8(42.1%)
No Hepatocellular Carcinoma	253(96.6%)	136(53.8%)	117(46.2%)

186 Patients were stratified to Child Pugh Class-A being on double regimen for 12 weeks. Of which 175 (94%) achieved SVR whereas out of 76 patients being in decompensated liver cirrhosis stage on triple regimen classified as Child Pugh Class B gave an SVR of 68(89.5%). The relative division of efficacy in term of SVR and HCC in both the groups is shown in Table-II.

Table-II: Sustained Virological Response and Hepatocelluar Carcinoma in Double and Triple Regimen (n=262)

Sustained Virological Response Achieved			No Sustained Virological Response Achieved			*p*-value	Hepatocellular Carcinoma			No Hepatocellular Carcinoma			*p*-value
Male	Female	Total	Male	Female	Total		Male	Female	Total	Male	Female	Total	
Child-Pugh Class-A + double regimen for 12 weeks													
98(56%)	77(44%)	175	7(64%)	4(36%)	11	0.191	1(100%)	0	1	104(56%)	81(44%)	185	0.000
Child-Pugh class B + triple regimen for 24 weeks													
32(47%)	36(53%)	68	4(50%)	4(50%)	8	0.191	4(50%)	4(50%)	8	32(47%)	36(53%)	68	0.000

Post Stratification Chi-Square proved to have significant relationship with use of DAA and occurrence of HCC both with double and triple regimens. (*p*-value <0.001).

162(61.8%) of the patients were previously treated with interferon and 100(38.2%) were treatment naïve. 50(19.1%) of the parteners were also positive and (80) 30.5% had history of blood transfusion. 36(13.7%) patients were drug abusers and all of them were male. The Distribution of these factors in the history among both the gender are explained in figure.

However gender was not associated with HCC occurrence. (*p*-value=0.915). Other charecteristics which were studied in the history of the patients were compared with occurrence of hepatocellualar and followings relations were found.

Table-III: Association of Various Factors with Hepatocellualar Carcinoma (n=262)

Variables	Hepatocellualr Carcinoma		*p*-value
	Yes	No	
Gender			
Male 141(53.8%)	5	136	0.915
Female 121(46.2%)	4	117	
Partner History of HCV			
Positive	9	203	0.138
Negative	0	50	
Drug Abuser			
Yes 36	1	35	0.816
No 226	8	218	
History of Blood Transfusion			
Yes	5	75	0.97
No	4	178	
Sustained Virological Response			
Achieved 243(92.7%)	6	237	0.002
Not Achieved 19(7.3%)	3	16	
Interferon Treated			
Yes 162(61.8%)	8	154	0.001
No 100(38.2%)	1	99	

DISCUSSION

Cancer related mortality has been greatly contributed by HCC which is the commonest primary liver malignancy. HBV and HCV are the leading causes contributing to it; in addition to alcohol abuse and NASH. HCV, a blood borne infection affecting liver, is emerging and has increased HCC prevalence.[11,12] In order to cope with this deadly disease, DAA has been introduced after getting lesser efficacy and tolerability with INF.DAA are now being used to treat HCV due to better efficacy, easy tolerability, lesser side effects and good compliance. The real problem with their use is development of HCC after its use.

In our study, 9(3.4%) of treated patients developed HCC. In other study by by Calvaruso *et al.* the incidence of HCV was found to be 3.5 % which is comparable to our study.[13] This percentage is in contrast to Conti *et al.* and Tayyab *et al.* who reported HCC incidence of 7.5 % and 12.5% respectively after the use of DAA.[2,10] There are few other studies showing conflicting results and has reported either a decrease or similar rate of HCC after DAA use.[14,15] The concept of increased HCC risk after DAA was further studied in detail, with larger sample size and much longer follow ups in other studies. These studies showed a decreased risk of HCC with use of DAA.[16,17]. Our study has supported the evidence of increased HCC occurrence which has also been supported by other studies.[18,9] This demands for an extensive research to be made on the topic to resolve the mystery especially focusing on genotype 3a.

Out of 262, 243(92.7%) achieved SVR. This clearly depicts excellent effectiveness of DAA in treating HCV patients both at compensated and decompensated stage of cirrhosis. This is comparable to two local studies which reported an SVR of 91.9% and 96.6%. However latter study included only treatment naïve patients without decompensated liver disease.(Zahoor *et al.* and Tayyab *et al*).

This risk was even greater with use of triple regimen. Of 9 patients developing HCC, 8 were on triple regimen signifying a greater risk for HCC by use of triple regimen.All these patients were of Child Pugh Class-B which means chances of developing HCC after use of DAA are greater in patients with advanced cirrhosis. This was explained in a study that reported HCC incidence of 2.1% with Child Pugh Class-A and 6.6% incidence with Child Pugh Class-B which is consistent with our findings as well.(Conti *et al.*) This depicts a fact that advanced cirrhotic liver has greater tendency to develop into HCC. This is in accordance to literature. However HCC is not dependant on cirrhosis only and can occur in the absence of cirrhosis as well. This shows the role of other factors in contributing HCC development.[19] Possible cause for tumor in these patients is not well understood. Several theories pose it to be either due to change in immunosurveillance or gene expression.[20,21]

Here we have highlighted an important aspect pertaining to the use of DAA, which are being used frequently to treat HCV. DAA are posing a serious threat to mankind in the form of HCC. Judicious use of DAA along with continuous monitoring for HCC of

patient on DAA is recommended.The literature was suggestive of less chances of HCV with use of INF and improved cirrhosis which gives an idea of using INF with a single DAA rather than a triple regimen that poses a greater threat for HCC.[22] This requires an extensive research to be made on this matter, in order to develop a gold standard regimen with good efficacy, better tolerability and lesser threat of developing HCC with its use.

CONCLUSION

DAA are effective against 3a genotype of Hepatitis C in Pakistan in terms of achieving SVR. However, There is an increased risk of HCC with their use. So, They are recommended for treatment of HCV with caution and serial monitoring during and after the treatment.

Conflict of Interest: None

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

SZ & SA: Data acquisition, data analysis, concept, critical review, approval of the final version to be published.

MAS & SZ: Critical review, data acquisition, drafting the manuscript, approval of the final version to be published.

KA & SA: Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investi-gated and resolved.

REFERENCES

1. Baumert TF, Jühling F, Ono A, Hoshida Y. Hepatitis C-related hepatocellular carcinoma in the era of new generation antivirals. BMC Med 2017; 15(1): 52.
2. Guo L, Wang Z, Du Y, Mao J, Zhang J, Yu Z et al. Random-forest algorithm based biomarkers in predicting prognosis in the patients with hepatocellular carcinoma. Cancer Cell Int 2020; 20(1): 1-2. https://doi.org/10.1186/s12935-020-01274-z
3. Wirth TC, Manns MP. The impact of the revolution in hepatitis C treatment on hepatocellular carcinoma. Ann Oncol 2016; 27(8): 1467-1474.
4. Zahoor S, Hameed S, Zahoor S, Jehangir HM, Firdous S. Efficacy of sofosbuvir in the treatment-naïve patients infec-ted with 3a genotype of Hepatitis C. Prof Med J 2020; 28(01): 72-79.
5. Conti F, Buonfiglioli F, Scuteri A, Crespi C, Bolondi L, Caraceni P, et al. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. J Hepatol 2016; 65(4): 727-733.
6. Steinebrunner N, Sprinzl MF, Zimmermann T. Early virological response may pre-dict treatment response in sofosbuvir-based combination therapy of chronic hepatitis c in a multi-center "real-life" cohort. BMC Gastroenterol 2015; 15(1): 97-100
7. Brown Robert S J. The possible association between DAA treatment for HCV infection and HCC recurrence. Gastroenterol & hepatol 2016; 12(12): 776.
8. Yang JD, Aqel BA, Pungpapong S, Gores GJ, Roberts LR, Leise MD, et al. Direct acting antiviral therapy and tumor recurrence after liver transplantation for hepatitis C-associated hepatocellular carcinoma. J Hepatol 2016; 65(4): 859-860.
9. Cardoso H, Vale AM, Rodrigues S, Gonçalves R, Albuquerque A, Pereira P, et al. High incidence of hepatocellular carcinoma following successful interferon-free antiviral therapy for hepatitis C associated cirrhosis. J Hepatol 2016; 65(5): 1070-1074.
10. Tayyab GU, Rasool S, Nasir B, Rubi G, Abou-Samra AB, Butt AA, et al. Hepatocellular carcinoma occurs frequently and early after treatment in HCV genotype 3 infected persons treated with DAA regimens. BMC Gastroenterol 2020; 20: 1-7.
11. Afzal MS. Hepatitis C virus and interferon-free antiviral therapeutics revolution: implications for Pakistan. Viral Immunol 2017; 30(4): 252-257.
12. Zafar A, Imran M, Zahoor S, Shah ZH, Ali M, Afzal MS, et al. Prevalence and treatment of untypable HCV variants in different districts of Punjab, Pakistan. Viral Immunol 2018; 31(6): 426-32.
13. Calvaruso V, Cabibbo G, Cacciola I, Petta S, Madonia S, Bellia A, et al. Incidence of hepatocellular carcinoma in patients with HCV associated cirrhosis treated with direct-acting antiviral agents. Gastroenterol 2018; 155(2): 411-421.
14. Li DK, Ren Y, Fierer DS, Rutledge S, Shaikh OS, Lo Re III V, et al.. The short-term incidence of hepatocellular carcinoma is not increased after hepatitis C treatment with direct-acting antivirals: An ERCHIVES study. Hepatol 2018; 67(6): 2244-2253. https://doi.org/10.1002/hep.29707
15. Huang P, Liu M, Zang F, Yao Y, Yue M, Wang J, et al. The development of hepatocellular carcinoma in HCV-infected patients treated with DAA: a comprehensive analysis. Carcinogenesis. 2018; 39(12): 1497-1505. https://doi.org/10.1093/carcin/bgy099
16. Ioannou GN, Green PK, Berry K. HCV eradication induced by direct-acting antiviral agents reduces the risk of hepatocellular carcinoma. J Hepatol 2018; 68(1): 25-32.
17. Innes H, Barclay ST, Hayes PC, Fraser A, Dillon JF, Stanley A, et al. The risk of hepatocellular carcinoma in cirrhotic patients with hepatitis C and sustained viral response: role of the treatment regimen. J Hepatol 2018; 68(4): 646-654.
18. Yang JD, Aqel BA, Pungpapong S, Gores GJ, Roberts LR, Leise MD, et al. Direct acting antiviral therapy and tumor recurrence after liver transplantation for hepatitis C-associated hepatocellular carcinoma. J Hepatol 2016; 65(4): 859-860.
19. Mittal S, El-Serag HB, Sada YH, Kanwal F, Duan Z, Temple S, et al. Hepatocellular carcinoma in the absence of cirrhosis in United States veterans is associated with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2016; 14(1): 124-131.
20. Villani R, Vendemiale G, Serviddio G. Molecular mechanisms involved in HCC recurrence after direct-acting antiviral therapy. Int J Mol Sci 2019; 20(1): 49.
21. Grandhe S, Frenette CT. Occurrence and recurrence of hepatocellular carcinoma after successful direct-acting antiviral therapy for patients with chronic hepatitis C virus infection. Gastroenterol Hepatol 2017; 13(7): 421.
22. Nahon P, Layese R, Bourcier V, Cagnot C, Marcellin P, Guyader D, et al. Incidence of hepatocellular carcinoma after direct antiviral therapy for HCV in patients with cirrhosis included in surveillance programs. Gastroenterol 2018; 155(5): 1436-1450.