Research Article

Sofosbuvir-Velpatasvir for Chronic Hepatitis C Virus-Infected Children and Young Adults: Efficacy and Safety

Attique Abou Bakr,[1] Shahid Sarwar,[2] Naeem Aslam,[3] Mamoona Ghias,[4] Imran Mehfooz[5]

[1,2]Department of Gastroenterology, AIMC/ Jinnah Hospital Lahore; [3]Department of Gastroenterology, Mayo Hospital Lahore; [4,5]Department of Medicine, King Edward Medical University Lahore.

Abstract

Background: Sofosbuvir-Velpatasvir has a high efficacy in adult patients with chronic hepatitis C infection .In this study, we reported treatment outcome with this drug in children and younger adults in Pakistani population.

Objective: To assess the efficacy and safety of Sofosbuvir-velpatasvir in treating HCV-infected children and young adults.

Methods: This Interventional(Clinical trial) was done in Hepatitis clinic Jinnah Hospital, Lahore from April 10, 2021 to January 9, 2022.A total of 45 patients aged 6 to 18 years with detectable HCV RNA by PCR were registered. They were evaluated clinically. HCV genotyping was not done as Sofosbuvir – Velpatasvir is pangenotypic. All of the patients were given a single oral dose of Sofosbuvir-velpatasvir per day. Ribavirin was included for patients with compensated cirrhosis and for those who were treatment-experienced .Clinical assessment, CBC, LFT, RFT, and PT were performed monthly to determine side effects and safety. To evaluate treatment efficacy, HCV RNA was measured by PCR at 12 weeks (end of treatment) and 12 weeks post-treatment (sustained virological response). Treatment lasted for 24weeks for those with compensated cirrhosis. (Child Turcotte Pugh score 5 and 6; Child class A) or those who were treatment experienced. SPSS 24 was used for data analysis.

Results: Non cirrhotic patients had a mean age of 13.6±1.45 years, while those with compensated cirrhosis had 14.1±2.15 years. There were 63.6% males (28) and 36.4% female (17). 41 patients (91.11%) had undetectable HCV RNA by PCR, 12 weeks after treatment (Sustained virological response), indicating treatment effectiveness. Nine patients had HBV co-infection and took HBV medications as well during HCV treatment. At 12 weeks post-treatment, all HBV-coinfected patients had undetectable HCV RNA by PCR and lower HBV titers. Some of the patients experience minor side effects. However, none of the patients stopped their treatment due to these side effects Thus, this treatment was safe and effective.

Conclusion: Sofosbuvir/velpatasvir has effectiveness and safety in treating HCV in children and young adults.

Corresponding Author | Dr. Attique Abou Bakr, Assistant Professor, Gastroenterology, AIMC/ Jinnah Hospital, Lahore
Email: doctorattique07@yahoo.com

Keywords | Hepatitis C virus , Direct acting antivirals, Sofosbuvir-velpatasvir.

Production and Hosting by KEMU
https://doi.org/10.21649/akemu.v29i2.5442

Introduction

The spread of the hepatitis C virus (HCV) is now recognized as a major public health issue worldwide. Over 71 million people worldwide are afflicted with this virus. HCV antibodies were found in 13.2

million youngsters in a recent study.[1] After the first direct-acting antiviral medication (DAA) was approved in 2011, HCV treatment has advanced significantly.[2] More than ten different drug combinations have been approved for the treatment of HCV in adults. With 12 weeks of treatment, these regimens can achieve SVR in >90% of cases. Sofosbuvir-velpatasvir was approved for adults in June 2016 and for children aged 6-17 and 3-5 years in March 2020 and June 2021, respectively.[3,4] Joehl Nguyen et al demonstrated the cost-effectiveness of DAA in children aged 12. Jonas MM et al. in their study on 173 children, 6 to 18 years of age with sofosbuvir-velpatasvir found SVR 12≥ 92% across genotypes 1,2,3,4 and 6.[21] Given the aforementioned, we examined the efficacy and safety of this combination in treating children over six years old in Pakistan, as to our knowledge no analogous study exists in our population. So this determination can play an important role in making our local guidelines regarding the treatment of children and may help in eradicating the disease and reducing the financial burden on our healthcare system.

Methods

The study's sample size was 45 patients with a 2% margin of error and a 95% confidence level with 80% power of test and taking an expected percentage of efficacy as 90% with Sofosbuvir-Velpatasvir.

This Interventional study involved 45 HCV-infected children/young adults referred to the Hepatitis clinic Jinnah Hospital Lahore from April 2021 to January 2022 and their relevant data was recorded. Drug dosage, duration, and side effects and efficacy were determined during and after treatment. We have prepared our own questionnaire based on CLDQ[22] (chronic liver disease questionnaire) .Quality of life in CLD can be evaluated with the help of the CLDQ, which is a disease-specific, well-validated questionnaire. This questionnaire has been pretested in international studies[22] and its chronbach's alpha value is 0.8 .There are 29 total items in it, and they cover digestive issues, lack of energy, systemic symptoms, activity, anxiety and emotional function. The CLDQ results produced a 7-point scale, from "always" to "never," covering the range of possible CLDQ responses. This study only included non-cirrhotic and compensated cirrhosis (Child A) and advanced disease cases with liver decompensation (Child B and C) were excluded.

Children and adults aged 6–18 with detectable HCV RNA by PCR were included. They included treatment naïve and experienced individuals. Clinical assessment, CBC, LFT, RFT, PT and Ultrasound abdomen were done at the start of study and after each month during treatment to assess side effects, safety and fitness of patients for treatment and to exclude decompensated disease from noncirrhotic and compensated disease

The patients received Sofosbuvir 400 mg-velpatasvir 100mg daily for 12 weeks (non cirrhotic or treatment Naïve) or 24 weeks(compensated cirrhosis or treatment experienced). Patients under 12years or <30kg received half the dose. (total 32 patients).[3] Treatment-experienced/ compensated cirrhosis patients received Ribavirin 10-15 mg/kg/day[5,9] and had their CBC tested at the end of the 2nd week, 4th, 8th, and 12th weeks. At 4, 8, and 12 weeks of treatment, patients were interviewed in person or by phone about drug side effects like headache, oropharyngeal pain, sinusitis, diarrhea, abdominal discomfort, nausea, vomiting, pyrexia, cough and lethargy. Older children and young adults themselves communicate with the interviewers and younger children were accompanied by their guardians and they also helped out in interview process. Interview bias were handled by making a panel of multiple people who interview the patients, using interview guide and standard questionnaire, full noting of answers, reducing chit chat during interview, recruitment from different places and building a diverse shortlist. To measure treatment efficacy, HCV RNA by PCR was done. End-of-treatment response (undetectable HCV RNA by PCR at the end of treatment; ETR) and Sustained Virological Response (undetectable HCV RNA by PCR after 12 weeks of therapy; SVR12) were assessed. In cases of compensated cirrhosis or in patients who were treatment-experienced, the total duration of therapy was increased to 24 months. For quantitative data like age, mean and standard deviation were determined. For qualitative variables like gender and treatment response/efficacy (ETR and SVR12), frequency and percentages were calculated.

SPSS 24 was used for data analysis.

Results

Out of 45 patients, the mean age was 13.6±1.45 years in non-cirrhotics and 14.1±2.15 years in compensated cirrhosis. There were 63.6% boys (28), and 36.4% girls

Table 1: *Different Characteristics of Patients without Cirrhosis and in Compensated Cirrhosis*

Variable	Patients without Cirrhosis	Patients with compensated cirrhosis	Total
Age (mean ± Standard Deviation)	13.6±1.45 years	14.1±2.15 years	
Gender	18 boys (40.89%), 11 girls (23.55%).	10 boys(22.71) 6girls(12.85)	28 boys (63.6%), 17 girls (36.4%).
Child Class A patients	-	16	
Child Turcotte Pugh score	-	5.87±0.52	
Treatment experienced	-	9	
Alanine aminotransferase (U/L)	56.22 ±34.53	58.92 ±9.86	
Total bilirubin (mg/dL)	0.92 ±0.28	0.98 ±0.49	
Hemoglobin (g/dl)	13.84±2.69	12.48 ±2.67	
Serum creatinine (mg/dL)	0.78 ±0.42	0.87 ±0.26	
Platelets $\times 10^3$ /mm	264.37 ±67.66	116.88 ±22.24	

Table 2: *Treatment Efficacy of Sofosbuvir-Velpatasvir in the Study*

Treatment response/ Efficacy	Non cirrhosis patients, n		Compensated cirrhosis patients,n		Treatment Response
	Yes	No	Yes	No	
End-of-treatment response	27	2	14	2	91.11%
Sustained virological response	27	2	14	2	91.11%

Table 3: *Adverse Effects of Sofosbuvir-Velpatasvir Treatment*

Side effects	Patients without cirrhosis,n	Patients with compensated cirrhosis,n
Diarrhea	1	2
abdominal pain,	2	3
headache,	1	0
vomiting,	3	2
nausea,	3	2
fatigue,	2	3
pyrexia,	0	1
cough,	2	3
oropharyngeal pain	1	2
sinusitis	1	3
Anemia	2 (2.1%)	11 (28.9%)
Platelets<90mmx10^3/mm^3	4 (4.2%)	8 (21.05%)
TLC <4x10	0	3
Total bilirubin >2.5X ULN	0	0

(17)., The Referral from Haematology/ Oncology ward accounted for 66.93% (31 patients), all of whom had received blood products previously. Two patients had surgical history, three patients had the unknown source of infection. 11 patients (23.75%) were treatment experienced with INF. 4 patients were HCV-HBV confected and were also treated with Entecavir or Tenofovir along with antiviral treatment for Hepatitis C. ETR and SVR12 was achieved in 41 patients (91.11%). Remaining 4(8.89%) had got decrease in HCV RNA by PCR by 1-2 log but RNA still remained detectable at the end of treatment. After 24 weeks of antiviral treatment, RNA was undetectable in patients with compensated cirrhosis. HCV-HBV co-infected and treatment experienced individuals had a negative HCV PCR, 12 weeks after treatment. Patients reported no serious adverse effects. The different characteristics of patients, treatment efficacy and side effects are explained in Table 1, 2 and 3.

Discussion

This study evaluates the efficacy and safety of Sofosbuvir-Velpatasvir in children and young adults of the Pakistani population. This combination for 12 weeks was found to be highly effective and well-tolerated in pediatric patients without cirrhosis or with compensated cirrhosis In this trial, as in other studies conducted in developing countries, transfusion of blood products was revealed to be the leading cause of HCV acquisition.[7-9] Due to efficient blood screening in affluent countries, vertical transmission is the main route of infection. HBV co-infection is a risk factor for early morbidity. Since DAA treatment may trigger a flare-up of HBV, all patients with HBV co-infection got concurrent anti-HBV medication during HCV treatment and or up to three months following it.[12,13] To analyze the effectiveness in relation to viral load, a larger sample size is required. A good response to INF-based therapy is predicted by a decreased viral load, but few studies have been done in connection with the DAA.[14-16] The treatment in the current study was well tolerated except for minor side effects. However, none of the patients stopped their treatment due to these side effects. SVR 12 in our study was 91.11%, which shows a considerable improvement as compared to INF based treatment where SVR was up to 64% .[17] A study from Taiwan showed

similar results.[3,4,18] In treatment-experienced/ compensated cirrhosis patients, the 24-week regimen yielded similar results.[19] Data is scarce on the studied subject in our country. However, there are some caveats to our study; small sample size, genotyping was not done as treatment regimen is pangenotypic and due to cost issues. The study included non-cirrhotic patients and those with compensated cirrhosis (Child class A), but had not included patients with hepatic decompensation. Most of the patients were treatment naïve. These limitations should be addressed in further studies that need to include decompensated patients with large sample sizes.

Our study highlights the need to ensure safe blood screening and transfusion practices.

Conclusion

Sofosbuvir/velpatasvir treats HCV infection in young adults and teens without cirrhosis and those with compensated cirrhosis safely and effectively. This medicine works well for both untreated and previously treated patients who did not respond.

Ethical Approval: Given
Conflict of Interest: The authors declare no conflict of interest.
Funding Source: None

References

1. Global hepatitis report, 2017 [Internet]. World Health Organization; [cited 2023 Jul 18]. Available from: https://www.who.int/publications-detail-redirect/9789241565455
2. Indolfi G, Hierro L, Dezsofi A, Jahnel J, Debray D, Hadzic N et al. Treatment of Chronic Hepatitis C Virus Infection in Children. A Position Paper by the Hepatology Committee of European Society of Paediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr. 2017;66(3):1. doi: 10.1097/ MPG.0000000000001872
3. AASLD/IDSA HCV guidance: recommendations for testing, managing, and treating hepatitis C [Internet]; 2021. [cited 2021 Aug 9]. Available from: http:// hcv-guidelines.org/ [Google Scholar]
4- Commissioner O of the. FDA approves new treatment for pediatric patients with any strain of hepatitis C [Internet]. FDA; [cited 2023 Jul 18]. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-pediatric-patients-any-strain-hepatitis-c
5. Pawlotsky JMP, Aghemo A, Back D, Dusheiko G, Forns X, Negro F et al. EASL Recommendations on Treatment of Hepatitis C 2016. J Hepatol. 2017;66(1):153–194. doi: 10.1016/j.jhep.2016.09.001
6. Squires JE, Balistreri WF. Hepatitis C Virus Infection in Children and Adolescents. Hepatol Commun. 2017; 1(2):87–98. doi: 10.1002/hep4.1028
7. El-shabrawi MH, Kamal NM. Burden of pediatric hepatitis C. World J Gastroenterol. 2013; 19(44): 7880–8. doi:10.3748/wjg. v19.i44.7880
8. El-Guindi MA. Hepatitis C Viral Infection in Children: Updated Review. Pediatr Gastroenterol Hepatol Nutr. 2016;19(2):83–95. doi: 10.5223/pghn.2016.19.2.83
9. Daw MA, Dau AA. Hepatitis C virus in Arab world: a state of concern. Sci World J. 2012;2012:719494. doi: 10.1100/2012/719494
10. Hussein NR, Tunjel I, Basharat Z, Taha A, Irving W. The treatment of HCV in patients with haemoglobinopathy in Kurdistan Region, Iraq: A single centre experience. Epidemiol Infect. 2016;144(8):1634–1640. doi:10.1017/ S0950268815003064
11. Mohamoud YA, Riome S, Abu-raddad LJ. International Journal of Infectious Diseases Epidemiology of hepatitis C virus in the Arabian Gulf countries: Systematic review and meta-analysis of prevalence. Int J Infect Dis. 2016;46(1):116-125. doi: 10.1016/j. ijid. 2016. 03. 012
12. Aggeletopoulou I, Konstantakis C, Triantos C, Manolakopoulos S. Risk of hepatitis B reactivation in patients treated with direct-acting antivirals for hepatitis C. World J Gastroenterol. 2017;23(1):4317–4323. doi: 10.3748/wjg.v23.i24.4317
13. Wang C, Ji D, Chen J, Shao Q, Li B, Liu J et al. Hepatitis due to Reactivation of Hepatitis B Virus in Endemic Areas Among Patients With Hepatitis C Treated With Direct-acting Antiviral Agents. Clin Gastroenterol Hepatol. 2017;15(1):132–136. doi: 10.1016/ j.cgh. 2016. 06.023
14. Liu CJ, Chuang WL, Sheen IS, Wang HY, Chen CY, Tseng KC et al. Efficacy of Ledipasvir and Sofosbuvir Treatment of HCV Infection in Patients Coinfected With HBV. Gastroenterology. 2018;154(4):989–997. doi: 10.1053/j.gastro.2017.11.011
15. Aziz H, Athar MA, Murtaza S, Irfan J, Waheed Y, Bilal I et al. Predictors of response to antiviral therapy in patients with chronic hepatitis C from Pakistani population. Chin Med J (Engl). 2011;124(9):1333–13337.

doi: 10.3760/cma.j.is sn.0366-6999.2011.09.011

16. Taylor JG, Zipfel S, Ramey K, Vivian R, Schrier A, Karki KK et al. Discovery of the pan-genotypic hepatitis C virus NS3/4A protease inhibitor voxilaprevir (GS-9857): A component of Vosevi®. Bioorganic & Medicinal Chemistry Letters. 2019 Aug 15;29(16):2428-36.
17. Schwarz KB, Karnsakul W. Treatment of Hepatitis C in Children. Curr Hepatol Reports. 2017;16(1):18–25. doi: 10.1007/s11901-017- 0334-1 24
18. Llaneras J, Riveiro-Barciela M, Lens S, Diago M, Cachero A et al. Effectiveness and safety of sofosbuvir/velpatasvir/voxilaprevir in patients with chronic hepatitis C previously treated with DAAs. Journal of hepatology. 2019 Oct 1;71(4):666-72.
19. Rosenthal P, Schwarz KB, Gonzalez-Peralta RP, Lin CH, Kelly DA, Nightingale S, Balistreri WF, Bansal S, Jonas MM, Massetto B, Brainard DM. Sofosbuvir and ribavirin therapy for children aged 3 to< 12 years with hepatitis C virus genotype 2 or 3 infection. Hepatology. 2020 Jan;71(1):31-43.
20. Cost Effectiveness of Early Treatment with Direct-Acting Antiviral Therapy in Adolescent Patients with Hepatitis C Virus Infection. J Pediatr. 2019 Apr; 207 (1): 90-96. doi: 10.1016/j.jpeds.2018.12.012. Epub 2019 Feb 6.
21. Safety and efficacy of sofosbuvir/velpatasvir in pediatric patients 6 to <18 years old with chronic hepatitis C infection [abstract 748]: HCV guidance [Internet]. [cited 2023 Jul 18]. Available from: https:// www. hcvguidelines. org/references/jonas-2019a
22. Sobhonslidsuk A, Silpakit C, Kongsakon R, Satitpornkul P, Sripetch C. Chronic liver disease questionnaire: translation and validation in Thais. World J Gastroenterol. 2004 Jul 1;10(13):1954-7. doi: 10.3748/ wjg. v10. i13.1954. PMID: 15222044; PMCID: PMC 45 72238.