Safety of Sofosbuvir/Daclatasvir and Sofosbuvir/Ribavirin in Children and Adolescents with Chronic Hepatitis C

Abstract

Purpose Sofosbuvir/ribavirin and sofosbuvir/ledipasvir regimes are approved by European Association for Study of Liver (EASL) for Chronic Hepatitis C (CHC) infection in adolescents although none of the combinations is approved for age below twelve years. The aim of the study is to investigate the use of sofosbuvir/daclatasvir with or without ribavirin and sofosbuvir/ribavirin in children and adolescents with CHC infection.

Methods A single-centre, observational (off-label) study was performed. Patients with CHC and detectable HCVRNA, of either gender with age between three to seventeen years were included. Patients were given one of the two combinations; sofosbuvir/daclatasvir with or without ribavirin for 12 weeks and sofosbuvir/ribavirin for 24 weeks, according to the body weight. The patients were followed precisely for side effects of treatment and sustained virological response after twelve week (SVR12).

Results Fourteen patients were enrolled with mean age of 12.36 ± 5.43 years. Six (42.9%) were less than twelve years and eight (57.1%) were more than twelve years. Nine (64.28%) patients were given sofosbuvir/daclatasvir with or without ribavirin and five (35.71%) patients were given sofosbuvir/ribavirin. All fourteen (100%) patients achieved SVR12. No side effect was observed and normal growth was evaluated.

Conclusion The combination of sofosbuvir/daclatasvir with or without ribavirin showed high safety and efficacy in children and adolescents. Moreover, sofosbuvir/ribavirin combination also showed comparable safety and efficacy in age less than twelve years.

Key words Chronic Hepatitis C, Sofosbuvir, Daclatasvir, Ribavirin, Children, Adolescents.

Introduction

Hepatitis C virus (HCV) is the significant cause of chronic liver disease (CLD) which is estimated to affect 170 million people globally.(1) Chronic Hepatitis C (CHC) infection is described as persistence of serum HCVRNA for six months or more. (2) Rate of HCV seroprevalence in North America is 1% -1.5%, which is 0.17% for six to eleven years old and 0.39% for twelve to nineteen years old (3) and in the United States (US) affects 0.1% -2% children. (4) Its prevalence is estimated at 11.55% in adults and 1.6% in children in Pakistan. (5, 6)

HCV infection can be acquired by children mainly through vertical transmission and exposure of blood by transfusion and medical procedures. Overall incidence of vertical transmission is between 4.7% and 6.7%. (7-9) Maternal HIV infection increases this risk by two to three times. (8) Almost 25%-40% of infants and 6%-12% older children spontaneously clear their infection. (10) In this way, the majority of children (54% - 86%) with HCV will manifest CHC. (2) Most of the time the behaviour of the disease is usually inactive and symptomless in childhood, although in adolescents it has similar disease behaviour as adults, with twenty six times high risk of liver-associated mortality, hepatocellular carcinoma, and requirement for liver transplantation, compared to age-matched controls.

(10, 11) End stage liver disease (ESLD) and cancer due to CHC infection are rare during childhood, whereas, advanced liver fibrosis can progress slowly over time. Morbidity and mortality rates are significant in untreated CHC patients who develop subsequent clinical progression to ESLD. (12)

By the advent of direct acting antivirals (DAAs) for HCV, the complex CHC therapy is turned to an easy therapy with a few contraindications and side effects. In 2011, the US Food and Drug Administration (FDA) and the European Medicine Agency (EMA) recommended 08 oral DAA combinations for adults infected with CHC. Research within DAAs for children have been slower. (9) Moreover, pegylated interferon (PEG-IFN) and ribavirin have become outdated for CHC therapy irrespective of age. (13) Table 01 shows current recommended treatment options.

Currently, twelve week combination of sofosbuvir/daclatasvir is also an approved treatment option for CHC infection (all genotypes) in adults. This regimen is still neither been appropriately studied in adolescent patients nor approved to be given in younger children so the aim of this study is to assess the efficacy and safety of dual sofosbuvir/daclatasvir combination with or without ribavirin along with sofosbuvir/ribavirin combination in children.

METHODS

Study design and setting

A single-centre, observational (off-label), uncontrolled, prospective study was performed in outpatients at the department of Hepatology of Asian Institute of Medical Science hospital Hyderabad, Pakistan, from January 2016 to December 2018.

Study cohort

Patients with CHC and detectable HCVRNA irrespective of genotype, of either gender with age between three to seventeen years were included, after excluding pregnancy, end-stage renal disease (ESRD) or severe renal impairment (GFR <30 mL/min/1.73 m2), active malignancy or patient on chemotherapy and other causes of chronic liver disease.

Data collection and management

Patients' baseline demographic characteristics, sex, age, body weight and investigation i.e. complete blood count, prothrombin time, liver function test, albumen, creatinine, HCVRNA level and ultrasound abdomen were noted before the start of treatment. Cause of transmission were ascertained through detailed history and examination. Patients were randomly given one of the two combinations; sofosbuvir/daclatasvir with or without ribavirin for 12 weeks and sofosbuvir/ribavirin for 24 weeks, according to the body weight in kilograms; i.e. standard dose for patient with weight more than 34, half of the standard dose daily for patient weight between 17 to 34 and half of the standard dose on alternate days for patient's weight less than 17. Patients were followed precisely for side effects of treatment, very rapid virological response (vRVR) i.e. undetectable serum HCVRNA level at 2 weeks, and accordingly throughout the treatment and till SVR12 i.e. undetectable serum HCVRNA level after 12 weeks of completion of treatment. All the children were seen before, during and six months after SVR12 for any growth retardation and adverse events.

Data analysis

Data was entered and analysed using SPSS version 20.0. Descriptive statistical analysis was performed. Mean (SD)/ Median (IQR) was calculated as appropriate for all quantitative variables. Frequency with percentages were calculated for all categorical variables.

Ethical issues

The study started after the approval of the ethical review committee (***AIMS/ERCL/6344/15***) of the hospital. Written consent was obtained from the guardians before any treatment and intervention. All the data was collected through structured proforma.

RESULTS

Total number of fourteen patients were included in the study with mean age of 12.36 ± 5.43 years, six (42.9%) were less than twelve years and eight (57.1%) were more than twelve years. Mean weight was 35.29±19.59kg. Among these nine (64.28%) were males and five (35.7%) were females. One (7.1%) patient has compensated cirrhosis out of fourteen. Likely cause of transmission, 2 (14.3%) patient had history of ear-piercing, two (14.3%) patients' mothers were HCV positive likely vertical transmission, 1 (7.1%) patient had history of surgery, 1 (7.1%) patient visited dentist and one (7.1%) patient had history of blood transfusion, in seven (50%) patients no possible source of transmission found. (Table 02)

Baseline laboratory characteristics were compared in both treatment groups (Table 03) and p-value was calculated insignificant on the basis on T-Test. Ultrasound of liver showed normal, hepatomegaly and cirrhotic changes (Table 04).

Nine (64.28%) patients were given sofosbuvir/daclatasvir with or without ribavirin, of which seven (50%) patients were given sofosbuvir/daclatasvir with weight-based ribavirin and two (14.28%) patients were given sofosbuvir/daclatasvir without ribavirin. Five (35.7%) patients

were given sofosbuvir/ribavirin. Total thirteen (92.9%) patients achieved vRVR except one (7.1%) patient in sofosbuvir/ribavirin group (Table 05). All fourteen (100%) patients achieved SVR12 (Table 05). No side effect was observed and normal growth was evaluated.

DISSCUSSION

Curing HCV early—prior to their entry into childbearing years—is an important component of decreasing spread of HCV among entire population. Sofosbuvir/daclatasvir combination for twelve weeks in adults is a treatment option of CHC infection (all genotypes). Sofosbuvir/daclatasvir combination is not recommended by the FDA or EMA in children, and also recommendation regarding use of sofosbuvir/ribavirin in patients below 12 years of age is lacking.

In this study we offered sofosbuvir/daclatasvir to 9 (64.7%) patients matches to one of the pilot study performed at Egypt by El-Shabrawi MH et al in 2018 (14) but contradiction to our study their target population was only adolescent and treatment duration was only eight weeks, however we included children from three to seventeen years and duration was twelve weeks irrespective of genotype.

Another multicentre study from Egypt by Yakoot M et al in 2018 (15) reported with thirty patients between thirteen to seventeen years of age with CHC infection have been treated with sofosbuvir and daclatasvir in standard dose for twelve weeks with 100% SVR12 rate.

Recently, Abdel Ghaffar Ty et al in 2019 (16) from Egypt reported safety and efficacy of sofosbuvir and daclatasvir in genotype 4. Total forty CHC infected patients aged between eight to eighteen years or weight ≥17kg have been treated with standard and half of the standard dose according to weight >45kg and <45kg respectively, 45% of them were

children. The end of the treatment response (ETR), SVR12 and SVR24 were 97.5%, 97.5% and 95% respectively.

Further, second regime we offered was sofosbuvir/ribavirin to five (35.7%) patients which matches to one of the study by Almas M et al in 2017 (17) performed locally, patients mean age was 10.24 ±2.80 years. Blood transfusion and perinatal transmission were most common etiological factors, whereas, in our study mean age was 12.36 ± 5.43 and vertical transmission and procedures like ear-piercing, blood transfusion, dental procedure and surgery were most important etiological factors. Rapid virological response (RVR) and SVR12 were achieved by 30/35 (85.71%) and 34/35 (97.14%) patients respectively. Headache was observed in 8 (22.86%) patients. In our study vRVR was achieved by all patients except one (7.1%) patient, while SVR12 rate was 100% in our study with no drug related adverse reaction. Another study Wirth et al in 2017 (18) used same regime Sofosbuvir and Ribavirin, but all patients were above twelve years and were genomic specific taken only Genotype 2 (25%) GT3 (75%). Further, vertical transmission was most common aetiology (38.73%) and they randomised both treatment naïve and experienced patients with SVR12 rate was 98%.

Strength of the present study are the use of pan-genomic drug (Daclatasvir), inclusion of both population group on the basis of age more than twelve 12 years and less than12 years (most of the previous studies focused adolescent patients only). The study limitations are small sample size and conducted at a single centre. Therefore, the results can’t be generalized to whole population.

Conclusion

In conclusion, the combination of sofosbuvir/daclatasvir with or without ribavirin showed high safety and efficacy in children and adolescents. Moreover, sofosbuvir/ribavirin combination also showed comparable safety and efficacy in age less than twelve years.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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Genotype (GT)	AASLD, EASL, ESPGHAN
GT 1	Sofosbuvir (400mg) Ledipasvir (90mg) for 12 weeks
GT 2	Sofosbuvir (400mg) Ribavirin 15mg/kg for 12 weeks
GT 3	Sofosbuvir (400mg) Ribavirin 15mg/kg for 24 weeks
GT 4	Sofosbuvir (400mg) Ledipasvir (90mg) for 12 weeks
GT 5	Sofosbuvir (400mg) Ledipasvir (90mg) for 12 weeks

Legends of the tables

Table 01 Current recommendations for the treatment in adolescents (age >12 years or weight >35 kg).

Table 02 Baseline demographic & clinical characteristics.

Table 03 Baseline laboratory characteristics in both treatment groups.

Table 04 Ultrasound findings in both treatment groups.

Table 05 Virological response in both treatment groups.

GT 6	Sofosbuvir (400mg) Ledipasvir (90mg) for 12 weeks

Table 1 Current recommendations for the treatment in Adolescents (Age >12 years or Weight >35 kg).

AASLD: American Association for the Study of Liver Diseases, EASL: European Association for the Study of Liver, ESPGHAN: European Society of Paediatric Gastroenterology, Hepatology and Nutrition.

Table 02 Baseline demographic & clinical characteristics (n=14).

Age Mean (+/- SD) Years	12.36 +/- 5.43
Weight Mean (+/- SD) in Kg	35.29 +/- 19.59
Gender	1. Boys 9 (64.3%) 2. Girls 5 (35.7%)
Liver Status	1. Non-cirrhotic (92.9%) 2. Cirrhotic (7.1%)
Aetiology or Cause of Transmission	1. Ear-piercing (14.3%) 2. Vertical transmission (14.3%) 3. Surgery (7.1%) 4. Dental procedure (7.1%) 5. Blood transfusion (7.1%) 6. Not found (50%)
DAA Used	1. Sofosbuvir + daclatasvir+/- ribavirin (64.3%) 2. Sofosbuvir + ribavirin (35.7%)
Duration of treatment	1. 12 weeks (64.3%) 2. 24 weeks (35.7%)

DAA: directly acting antivirals.

Table 3: Baseline laboratory characteristics in both treatment groups.

	SOF/DAC/RBV (n=09)	SOF/RBV (n=05)	p-Value (0.05)
Haemoglobin (g/dL)	13.52	13.02	0.2

Platelets (per microliter)	275125	319500	0.12
Albumin (g/dL)	4.16	4.14	0.3
ALT (IU/L)	80.69	60.23	0.1
AST (IU/L)	56.58	36.2	0.08
PT (seconds)	12	12	0.5
Creatinine (mg/dL)	0.59	0.57	0.48
HCV RNA Quantitative (IU/L)	9165013.75	1401217.80	0.17

Values are presented as mean.

There were no significant differences between the two groups (All p>0.05).

SOF/DAC+/-RBV: sofosbuvir and daclatasvir with or without ribavirin, SOF/RBV: sofosbuvir and ribavirin, ALT: alanine transaminase, AST: aspartate transaminase, PT: prothrombin time, HCV RNA: hepatitis C virus ribonucleic acid.

Table 04: Ultrasound findings in both treatment groups.

	SOF/DAC/RBV (n=09)	SOF/RBV (n=05)	All (n=14)
Normal	6 (42.85)	3 (21.42)	9 (64.28)
Hepatomegaly	3 (21.42)	1 (7.14)	4 (28.57)
Cirrhotic Changes	0 (0%)	1 (7.14)	1 (7.14)

Values are presented as number (%).

SOF/DAC+/-RBV: sofosbuvir and daclatasvir with or without ribavirin, SOF/RBV: sofosbuvir and ribavirin.

Table 05. Virological response in both treatment groups.

	SOF/DAC+/-RBV (n=09)	SOF/RBV (n=05)	All (n=14)	p-value
vRVR	9 (100%)	4 (80%)	13 (90%)	0.58
SVR	9 (100%)	5 (100%)	14 (100%)	

Values are presented as number (%).

SOF/DAC+/-RBV: sofosbuvir and daclatasvir with or without ribavirin, SOF/RBV: sofosbuvir and ribavirin, vRVR: very rapid virological response, SVR: sustained virological response.