Original paper

The impact of sofosbuvir/ledipasvir on chronic hepatitis C-infected paediatric patients: a Middle East single-centre experience

Mohammad Fadhil Ibraheem, Falah Hasan Kareem

College of Medicine, University of Baghdad, Baghdad, Iraq

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Address for correspondence: Mohammad Fadhil Ibraheem, College of Medicine, University of Baghdad, Baghdad, Iraq, e-mail: mohammad68alqaisi@gmail.com

Abstract

Introduction: Direct-acting antiviral (DAA) regimens were approved in 2013 with a response rate exceeding 95% and minimal side effects. The response rate of sofosbuvir and ledipasvir exceeds 95% with minimal side effects.

Aim: To identify the effects of this regimen in the eradication of viruses from the patients.

Material and methods: A prospective observational, open-label study took place between July 2018 and September 2020. The study included 37 patients, about two-thirds of them were male 23 (62.16%), while females comprised 14 (37.84%). All patients received a combination of sofosbuvir 400 mg and ledipasvir 90 mg in a single oral daily dose according to their weight.

Results: The most common HCV genotype was HCV-4, followed by HCV-1 and HCV-2. And by comparing parameters at baseline, end of the treatment, and 12 weeks after completing the treatment, the laboratory data revealed dramatic drops of all liver function tests, the mean of alanine aminotransferase (ALT) (31.1 ±1.42 IU/l vs. 95.5 ±23.16, $p < 0.05$), aspartate aminotransferase (AST) (29.86 ±1.75 IU/l vs. 89.19 ±24.83, $p < 0.05$), total serum bilirubin (TSB) (0.57 ±0.07 mg/dl vs. 1.73 ±0.38 mg/dl, $p < 0.05$), mean HCV PCR (1605168 ±368223.72), after finishing the treatment course, and 12 weeks after that it was non-detectable ($p < 0.05$).

Conclusions: Treatment with dose-adjusted oral DAAs (SOF/LED) for 12 weeks was well tolerated in Iraqi children and adolescents infected with chronic HCV infections, with a high success rate and trivial adverse effects.

Introduction

There are 6 hepatitis C virus (HCV) genotypes, and all are implicated in paediatric populations [1]. HCV genotype 4 constitutes 12–15% (15–18 million) of the total global chronic HCV infection [2].

The prevalence of HCV in Iraqi patients is 0.4–2.8%, but it is much higher in some medical conditions that require extensive surgical manipulation or blood or blood product transfusion, and the most common HCV genotype is genotype 4 (in about 50% of the cases) followed by genotype 1 (in 43.3% of cases), and genotype 3 (6.7% of cases) [3–5].

The possibility of development of hepatocellular carcinoma (HCC) and severe liver disease in children is less common than in adults, but still HCV infection in children is not entirely benign, with reports of decompensated cirrhosis in young children with chronic hepatitis C (CHC). Children with HCV infection may also have developmental delay, learning disorders, cognitive deficits, and impaired quality of life [6].

Spontaneous resolution of CHC (2 negative RNA tests ≥ 6 months apart) may occur spontaneously or with treatment, but most of the children progress to develop CHC [7].

Direct-acting antiviral (DAA) regimens were approved in 2013 with a response rate exceeding 95% and minimal side effects for 12 weeks.

The response rate of sofosbuvir and ledipasvir is over 95% with minimal side effects in adults, and it was approved by the Food and Drug Administration (FDA) for application in adolescents aged 12–18 years with genotype 4 in 2017 [8, 9].

Many studies have shown this combination to be safe and effective in the age group of 6–11 years [10–12].

Although treatment in children aged between 3 and 6 years remains controversial because the possibility of progression to chronic liver disease is not known, infection transmission still exists, and the different studies done for this age group are encouraging regarding safety, effectiveness, and tolerability [13, 14].

Aim

The aim of this study was to identify the influence of sofosbuvir/ledipasvir on chronic hepatitis C-infected paediatric patients in a single centre between July 2018 and September 2020.

Material and methods

This is a prospective, observational, open-label study that took place between July 2018 and September 2020. The study included 37 patients recruited from the GIT and Hepatology Outpatient Clinic in the Children's Welfare Teaching Hospital, Medical City Complex, Baghdad.

A total of 37 consecutive patients, who had been detected from our HCV screening program prior to surgical procedure or discovered accidently following the discovery of unexplained elevated liver enzymes who fulfilled the inclusion criteria, were included in this study.

Inclusion criteria were children aged between 3 and 16 years, with HCV RNA analysis by polymerase chain reaction (PCR) results of more than 1.000 IU/l.

Patients were excluded from participating in the study if they had any of the following conditions: children older than 16 or younger than 3 years, viral load less than 1.000 IU/l, renal impairment, evidence of a malabsorption syndrome that could interfere with absorption of orally administered medications, patients with associated comorbidities such as hepatitis B virus infection, autoimmune hepatitis, Wilson's disease, any biliary disorder, hemolytic anaemia, or any malignancy or critical illness.

Parents provided written informed consent before the patients undertook any study-related procedures. Patients who could read and write provided written consent.

Six patients were excluded from the study; 3 patients with viral load lower than 1.000 IU/l, 2 patients had renal impairment, and one patient's parents refused to include him in the study.

The study was approved by the Ethical Scientific Committee of the Children's Welfare Teaching Hospital and was carried out according to the guidelines of the Helsinki Declaration [15].

All the patients were followed up for their laboratory parameters (which includes ALT, AST, TSB, S. alkaline phosphatase, HCV PCR, Hb level, WBCs, platelets, S. creatinine, and S. albumin) at the time of initiation of treatment (which continued for 12 weeks), when finishing the treatment, and at 12 weeks after the end of treatment (sustained virologic response 12, SVR12).

The families were advised to make immediate contact if any serious adverse effects developed at any time during the treatment.

The fibrosis stage was assessed by transient elastography (TE) Fibroscan® device (Echosens, Paris, France), which was performed in the GIT and Hepatology Hospital, Medical City Complex, Baghdad. The findings of at least 10 successful measurements and a success percentage of at least 60% were believed to be dependable and implicated in the study; the results (expressed in kilopascals) were categorized according to: < 7.1 kPa no or minimal fibrosis (F0-F1), 7.1–9.4 kPa moderate fibrosis (F2), 9.5–12.4 kPa severe fibrosis (F3), 12.5 kPa cirrhosis (F4), according to Lim *et al.* [16].

All patients received a combination of sofosbuvir 400 mg and ledipasvir 90 mg in a single oral daily dose if their weight was more than 35 kg, half the dose if their weight ranged between 17 and 35 kg, and a third of the dose if their weight less than 17 kg.

We followed the patients using HCV RNA analysis for the assessment of their response. The initial endpoint of this study was the loss of HCV RNA at the end of treatment (Week 12). The final endpoint was the loss of HCV RNA at 12 weeks following the end of treatment (SVR12).

The side effects of treatment were routinely documented during the treatment. Routine laboratory investigations were performed at baseline (prior to treatment) and followed up at week 12, and then 12 weeks after completing the treatment, which included full blood count, aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum bilirubin, and albumin levels, and serum creatinine.

HCV genotype was performed by direct sequencing of the 50 untranslated region (50 UTR) using a RT-PCR-based assay (AmpliSens HCVgenotype-FRT PCR kit) in the GIT and Hepatology Hospital, Medical City, Baghdad.

Statistical analysis

Data were collected and tabulated using the Statistical Package for the Social Sciences (SPSS) software version 20. Qualitative data were presented as counts and percentages. For quantitative data, descriptive statistics comprised the arithmetic mean, the standard deviation, the median, and the 95% CI whenever appropriate.

Results

Our study included 37 children and adolescents with chronic HCV; 23 (62.16%) were male and 14 (37.84%)

were female; all of the patients were treatment naive Eleven patients (29.73%) were aged 3–6 years, 21 (56.75%) patients were aged > 6–12 years, and 5 (13.52%) patients were aged > 12 years at the time of starting the treatment.

In 29 (78.37%) patients, HCV AB was positive, while 8 (21.63%) patients had a negative test result.

We found the most common HCV genotype to be HCV-4 in 24 (64.87%), followed by HCV-1 in 12 (32.43%) and HCV-2 in 1 (2.7%)

Transient elastography (Fibroscan) to determine the fibrosis stage revealed 17 (45.95%) with F0, 12 (32.43%) with F1, and 8 (21.62%) with F2, as shown in Table I.

By comparing the parameters at baseline, end of the treatment, and 12 weeks after completing the treatment, the laboratory data revealed dramatic decreases in all liver function tests: the mean alanine aminotransferase (ALT) before initiation of the treatment was 95.5 ±23.16 IU/l and fell to 31.1 ±1.42 IU/l after 12 weeks of the treatment; aspartate aminotransferase (AST) was 89.19 ±24.83 IU/l and by the end of the study it was 29.86 ±1.75 IU/l; serum alkaline phosphatase was 206.43 ±63.23 IU/l dropping to 33.35 ±3.33 IU/l; total serum bilirubin (TSB) was 1.73 ±0.38 mg/dl dropping to 0.57 ±0.07 mg/dl; and serum albumin was 2.81 ±0.28 gm/dl dropping to 3.84 ±0.17 gm/dl. Blood count parameters showed an increase during the study time, the mean haemoglobin (Hb) before initiation of treatment was 10.55 ±0.57 g/dl, which showed a significant increase 12 weeks after the end of the treatment, at 11.52 ±0.46 g/dl; white blood cells (WBC) from 6.5 ±0.71 × 10^3/mm^3 to 6.5 ±0.38 × 10^3/mm^3; platelet count from 278.730 ±50.75/mm^3 to 281.460 ±19.26/mm^3; serum creatinine (S. cr) from 1.429 ±0.39 mg/dl to 0.927 ±0.06 mg/dl; and serum albumin (S. alb) from 2.81 ±0.28 gm/dl to 3.84 ±0.17 gm/dl; while the mean HCV PCR was 1605168 ±368223.72, and after finishing the treatment course and 12 weeks after that it was non-detectable, as summarized in Table II.

Table I. Demographic and clinical criteria of the study cohort

Variable	*N* (%)
Age [years]:	
3–6	11 (29.73)
> 6–12	21 (56.75)
> 12	5 (13.52)
Gender:	
Male	23 (62.16)
Female	14 (37.84)
HCV AB:	
Positive	29 (78.37)
Negative	8 (21.63)
HCV genotype:	
1	12 (32.43)
2	1 (2.7)
4	24 (64.87)
Fibrosis stage Score by Fibroscan:	
F0	17 (45.95)
F1	12 (32.43)
F2	8 (21.62)

The side effects encountered in the study included tiredness in 11 subjects (29.72%), nausea in 6 (16.21%), headache and diarrhoea in 5 (13.51%), and difficulty sleeping in 2 (5.4%), as shown in Table III.

Discussion and conclusions

To the best of our knowledge, this is the first observational, open-labelled, single-centre study to assess the efficacy of a 12-week ledipasvir plus sofosbuvir

Table II. The mean of main biochemical and haematological tests at 3 time points

Variable [mean (95% CI)]	Pretreatment	At end of treatment	After 12 weeks of treatment	*P* value
Serum. ALT [IU/l]	95.5 ±23.16	49.45 ±6.86	31.1 ±1.42	< 0.05
Serum AST [IU/l]	89.19 ±24.83	45.8 ±6.97	29.86 ±1.75	< 0.05
T. bilirubin [mg/dl]	1.73 ±0.38	0.82 ±0.05	0.57 ±0.07	< 0.05
S. Alk. phosp. [IU/l]	206.43 ±63.23	54.1 ±6.65	33.35 ±3.33	< 0.05
HCV PCR [IU/ml]	1605168 ±368223.72	Not detected	Not detected	< 0.05
Haemoglobin [g/dl]	10.55 ±0.57	11.01 ±0.55	11.52 ±0.46	< 0.05
WBCs [× 10^3/mm^3]	6.5 ±0.71	6.1 ±0.55	6.5 ±0.38	< 0.05
Platelets [/mm^3]	278.730 ±50.75	301.100 ±28.35	281.460 ±19.26	< 0.05
Serum creatinine [mg/dl]	1.429 ±0.39	1.22 ±0.11	0.927 ±0.06	< 0.05
S. albumin [gm/dl]	2.81 ±0.28	3.23 ±0.19	3.84 ±0.17	< 0.05

Table III. Side effects encountered in the patients

Side effects	*N*	%	Duration of maximum period of complaint [weeks]
Tiredness	11	29.72	5
Nausea	6	16.21	3
Headache	5	13.51	8
Diarrhoea	5	13.51	7
Difficulty sleeping	2	5.4	3

regimen in children and adolescent treatment-naive patients infected with HCV in Iraq.

This study revealed that the regimen has a high rate of sustained virological response, is well tolerated, and with no discontinuation or death reported in this group of patients.

Anti-HCV antibody-negative results were found in 8 (21.63%) cases, and this may be related to the sensitivity of the test used, which was highly variable [17, 18]. Sometimes a negative result can be obtained when the test is performed too soon after exposure or if the patient has HIV, a donated organ, or other conditions that weaken the immune system, which can suppress the production of antibodies [19–21].

The most common HCV genotype found in this study was genotype 4 in 24 patients (64.87%), followed by genotype 1 in 12 (32.43%), and genotype 2 in 1 (2.7%).

It is estimated globally that genotype 1 accounts for more HCV cases than any other genotype, at 83.4 million (46.2%). HCV genotype 3 is the second most common and is estimated to account for 54.3 million (30.1%) cases globally.

Genotypes 2, 4, and 6 constitute the majority of the remaining cases of HCV worldwide, with an estimated 16.5 million (9.1%), 15.0 million (8.3%), and 9.8 million (5.4%) cases, respectively.

North Africa and the Middle East have the largest number of genotype 4 (65.3%) cases, followed by genotype 1 (27.3%) cases, while genotypes 2, 3, and 5 constitute the majority of the remaining cases, with an estimated 0.8%, 6.3%, and 0.3% of cases, respectively [22–24].

To the best of our knowledge, the current study is the first to assess DAAs in the young 3–16-year-old HCV-infected children in Iraq.

Although serious complications of chronic HCV infection in this age group, such as ascites, portal hypertension, variceal bleeding and hepatocellular carcinoma, are uncommon, they do occur; moreover, decompensated liver cirrhosis has been described in children as young as 4 years old, so it is better to start treatment of the patient as soon as possible [1].

High success rates of oral DAAs in the treatment of adolescents and children with chronic HCV have been reported in many studies for different genotypes; SVR12 ranged from 97% to 100% with trivial adverse effects and no fatalities [8, 10, 11, 13, 25].

The final result obtained from our patients who received 12 weeks of a single tablet of SOF/LED showed a high SVR12 of 100% with dramatic improvement of liver and renal function tests and full blood count.

El-Karaksy *et al.* in 2018 revealed that treatment with SOF/LED for 12 weeks was highly effective and well tolerated in Egyptian children and adolescents with chronic HCV infection, with an overall SVR12 rate of 100% [26], El-Shabrawi *et al*. in 2018 reported that treatment with SOF/LED for 12 weeks was highly effective in managing 6–12-year-old children with chronic HCV infection, with an overall SVR12 rate of 95% [11]; meanwhile, Balistreri *et al.* in 2017 [27] showed an SVR12 rate of 98% in treating adolescents with chronic HCV genotype 1 infection.

The marvellous success rate obtained in the study was associated with good tolerability and safety of the drug established by no fatalities and minimal adverse effects; mild tiredness was the most commonly reported side effect in less than one-third of the cases, followed by a much smaller percentage with nausea, headache, and diarrhoea, which is quite similar to what was observed in other studies [8, 13, 26–28].

These promising results obtained in children and adolescents are possibly attributed to the short duration of the disease as compared to adults with lower possibility of fibrotic and cirrhotic changes, which leads to less efficient results and less favourable long-term outcome of DAAs if initiated late after the development of advanced liver disease [8].

The dramatic outcome in this study may offer a strong new strategy and might pave the way for approval of DAAs in this age group to prevent new HCV infections by elimination the pool of infectious individuals.

In conclusion, treatment with dose-adjusted oral DAAs (SOF/LED) for 12 weeks was well tolerated in Iraqi children and adolescents infected with chronic HCV

infections, with a high success rate and trivial adverse effects.

Conflict of interest

The authors declare no conflict of interest.

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