Long-term Outcomes of Ledipasvir/sofosbuvir Treatment of Chronic Hepatitis C in Four Teenagers With Significant Liver Fibrosis

Maria Pokorska-Śpiewak (mpspiewak@gmail.com)
Medical University of Warsaw
Anna Dobrzeniecka
Regional Hospital of Infectious Diseases in Warsaw
Magdalena Marczyńska
Medical University of Warsaw

Research Article

Keywords: ledipasvir/sofosbuvir, chronic hepatitis C, transient elastography, liver fibrosis

Posted Date: June 24th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-650885/v1

Abstract

Long-term outcomes of therapy with ledipasvir/sofosbuvir (LDV/SOF) in children with chronic hepatitis C (CHC) and significant liver fibrosis were evaluated. Among 35 patients aged 12-17 years treated with LDV/SOF, there were four participants with significant fibrosis: one with a fibrosis score of F2 in the METAVIR scale, and three with cirrhosis (F4) evaluated with transient elastography (TE) at baseline. Patients were followed every 4 weeks during the treatment, at the end of the therapy, week 12 posttreatment, and one year after the end of treatment. One year after the end of treatment, the hepatitis C viral load was undetectable in three patients. In 2/4 patients, a significant regression of liver fibrosis was observed (from stage F4 and F2 to F0-F1 in the METAVIR scale). In one patient, the liver stiffness measurement median increased 12 weeks after the end of the treatment and then decreased but still correlated with stage F4. One patient was lost to follow-up after week 4. A one-year observation of teenagers with CHC and significant fibrosis treated with LDV/SOF revealed that regression of liver fibrosis is possible, but not obligatory. Further observations in larger groups of patients are necessary to find predictors of liver fibrosis regression.

Introduction

In the majority of cases, hepatitis C virus (HCV) infection in children leads to chronic hepatitis C (CHC) with a possible progression to serious liver disease. The risk of cirrhosis in HCV-infected children and adolescents was estimated at 1 to 2% [1–5]. However, a number of recent observational studies have demonstrated that a higher proportion of pediatric patients than had been previously thought may develop advanced liver disease resulting from HCV infection [6–8]. Turkova et al. demonstrated bridging fibrosis in 41% of their patients by histopathological evaluation with a median age of 10.4 years, and liver stiffness measurement (LSM) over 5.0 kPa in transient elastography (TE) evaluation in 30% of patients [7]. In addition, LSM increased by 0.09 kPa annually. Modin et al. analyzed the outcome of CHC in 1,049 patients infected with HCV during childhood and found that serious liver disease developed in 32% of cases with a median of 33 years after infection, irrespective of the mode of infection [8]. Thus, children infected vertically developed cirrhosis at an earlier age compared to patients infected from other sources, which is consistent with other observations [4]. The risk of HCV-related hepatocellular carcinoma (HCC) was 5%, the incidence of liver transplant was 4%, and the risk of death was 3% [8]. New highly effective interferon-free therapies for HCV infection based on direct-acting antivirals (DAAs) may be helpful for the prevention of long-term liver disease progression related to HCV by eliminating the virus [8,9]. In a recent systematic review with meta-analysis on the efficacy and safety of DAAs in children and adolescents, Indolfi et al. demonstrated that among the patients receiving all doses of treatment, 100% of cases reached a sustained virologic response (SVR) [9]. Among the subjects receiving at least one dose of DAA, the lowest efficacy rates were observed among cirrhotic patients (83%)[9]. However, only a few outcomes of DAA treatment in cirrhotic pediatric patients have been reported, and there is scarce and limited data on the influence of these therapies on liver fibrosis [9,10]. We recently reported that among our 35 patients [illegible] DV/SOF) treatment, 11% of cases presented

with significant fibrosis (F ≥ 2 in METAVIR scale), including 9% with cirrhosis [6]. Thus, in this paper, we aim to present the long-term outcomes of therapy in this specific group of patients. In particular, the influence of LDV/SOF treatment on the extent of liver fibrosis was analyzed.

Materials And Methods

Study group

In our single tertiary health care pediatric infectious disease center, consecutive HCV-infected patients aged 12–17 years treated between August 2019 and February 2020 were qualified for the *real-life* therapeutic program 'Treatment of Polish Adolescents with Chronic Hepatitis C Using Direct Acting Antivirals (*POLAC* PROJECT)'. Patients infected with genotypes 1 and 4 HCV were treated with sofosbuvir/ledipasvir (SOF/LDV), which was available courtesy of a donation by the pharmaceutical company. Patients with CHC (diagnosed in subjects with over a 6-month duration of disease confirmed with positive nucleic acid testing, HCV RNA, using a quantitative real-time polymerase chain reaction, RT-PCR, Abbott Real Time HCV, Abbott Laboratories, Abbott Park, Illinois, USA; measurement linearity range 12–1.0 x 10^8 IU/ml) were qualified for treatment irrespective of the extent of liver fibrosis or previous ineffective treatment. The duration of treatment was established according to the recommendations of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN): patients received 12 weeks of therapy unless they were infected with HCV genotype 1 with a history of previous ineffective interferon-based treatment and presented with cirrhosis [11]. Patients in this study were followed every 4 weeks during the treatment, at the end of the therapy, week 12 posttreatment (to assess the efficacy of the treatment based on a sustained virologic response, SVR12), and one year (52 weeks) after the end of treatment to assess long-term outcomes. Body mass index standard deviation (SD) scores (BMI z-scores) were calculated according to the WHO Child Growth Standards and Growth reference data using the WHO Anthropometric calculator AnthroPlus v.1.0.4. Obesity was diagnosed in children with a BMI z-score > 2 SD and overweight > 1 SD.

In this prospective study, we analyzed only a group of patients presenting with significant fibrosis (F ≥ 2 in METAVIR scale) established by transient elastography (TE) at the start of the treatment.

Transient elastography (TE)

TE was performed by trained examiners certified by the manufacturer, using the FibroScan device (Echosens, Paris, France). Two different probes were used: medium (M) and XL (for obese patients). TE was performed in patients who had fasted for at least 2 hours. Liver stiffness measurement (LSM) and controlled attenuation parameter (CAP) were simultaneously obtained. The adequacy of the measurement was assessed by the FibroScan device. The examination was considered successful when 10 valid measurements were conducted with at least a 60% success rate and an interquartile range (IQR) of less than 30% of the median LSM value [12]. The final LSM result was expressed as the median value of at least 10 valid measurements, and it was assessed in kilopascals (kPa). It corresponded to the liver

fibrosis in the METAVIR scale according to the Castera TE cutoffs as follows: no to mild fibrosis (F0-F1), LSM up to 7.0 kPa; moderate fibrosis (F2), LSM 7.1 to 9.4 kPa; severe fibrosis (F3), LSM 9.5 to 12.4 kPa; and cirrhosis (F4), LSM ≥ 12.5 kPa [13]. Liver fibrosis was considered significant if the LSM median was > 7 kPa, corresponding to a METAVIR F score ≥ 2 points. The final CAP values ranged between 100 and 400 decibels per meter (dB/m) and were assigned as follows: no steatosis (S0, CAP 0-238 dB/m); mild steatosis (S1, CAP 239–260 dB/m); moderate steatosis (S2, CAP 261–290 dB/m); and severe steatosis (S3, CAP > 290 dB/m) [10,14]. TE examination was performed three times: on the day the patient started treatment, week 12 posttreatment, and one year after the end of the treatment, simultaneously with the biomarker evaluation.

Biomarker evaluation

Biochemical serum testing was performed using commercially available laboratory kits. For both alanine and aspartate aminotransferase (ALT and AST) serum levels, 40 IU/L was considered the upper limit of normal (ULN). Two indirect fibrosis biomarkers were calculated, namely, the aspartate transaminase-to-platelet ratio index (APRI) and Fibrosis-4 index (FIB-4), according to the published analytic recommendations [15,16]:

APRI = [(AST (IU/L)/AST ULN)/Platelet count (10^9/L)] x 100

FIB-4 = [Age (years) x AST (IU/L)]/[Platelet count (10^9/L) x $\sqrt{ALT(IU/L)}$]

According to previously published data, the following cutoffs for the biomarkers were considered: APRI > 0.5 and FIB-4 > 1.45, which suggests significant fibrosis, and APRI > 1.5, which suggests cirrhosis [15,17].

Ethical Statement

Written informed consent was collected from all the patients and/or their parents/guardians before their inclusion in the study. The investigation was performed in accordance with the ethical standards in the 1964 Declaration of Helsinki and its later amendments. The local ethics committee by the Medical University of Warsaw approved this study.

Results

Participants

Among the 35 patients included in this therapeutic program, there were four patients aged 12–17 years with significant fibrosis: one presenting with a fibrosis score of 2 on the METAVIR scale and three with cirrhosis (F4 on the METAVIR scale). Their Child-Pugh class was A for all three cirrhotic patients. All four patients were infected vertically from an HCV-infected mother. Three subjects were infected with genotype 1b HCV and one with genotype 4. Patient 2 was coinfected with human immunodeficiency virus (HIV). All patients were treated with a fixed dose of 90 mg/200 mg LDV/SOF. Two patients were qualified

for a 12-week treatment, and two for a 24-week therapy. The baseline characteristics of these patients are presented in Table 1.

Treatment outcomes

Four weeks after the start of treatment, HCV viral load was below the lower limit of detection in three patients and undetectable in one patient. A decrease in the ALT level was observed in all four patients. At the end of the treatment, two patients had an undetectable HCV viral load, and it was unavailable in the remaining two subjects because their visits had to be cancelled due to the coronavirus disease-19 (COVID-19) pandemic. A similar situation was observed at 12 weeks posttreatment (SVR assessment). One year after the end of treatment, the viral load was undetectable in three patients, which confirmed the efficacy of the treatment. ALT levels in these patients were normal (Table 1). Patient No. 3 did not show up for the following visits after week 4 and was thus lost to follow-up.

The LDV/SOF therapy was well tolerated. No serious adverse events were observed. During the first 2 to 6 weeks of treatment, two patients reported headache, two reported fatigue, and one reported diarrhea, which resolved spontaneously.

Liver fibrosis and steatosis after the treatment

At week 12 posttreatment, a significant improvement in LSM in Patient 1 was observed, corresponding to a decrease from the F4 to F0-F1 stage on the METAVIR scale (Table 1). In Patient 2, the increase in LSM was from 14 to 33.6 kPa (F4). However, in both patients, a decrease in the APRI and FIB-4 values was observed (Table 1, Fig. 1). In Patient 1, LSM improvement was accompanied by a decrease in the CAP from S1 to S0, whereas in Patient 2, an increase in the CAP was found (Table 1, Fig. 1). Due to the COVID-19 pandemic, the 12-week posttreatment visits for Patients 3 and 4 had to be cancelled. Thus, data for these two patients were unavailable.

At the final visit, one year after completing the treatment, the LSM median corresponded to F0-F1 in Patients 1 and 4, whereas in Patient 2, the LSM was lower compared to the previous visit but still corresponded to an F4 score on the METAVIR scale. However, the APRI values decreased for all three of these patients (Table 1, Fig. 1). The CAP value for Patient 1 increased compared to the 12-week posttreatment visit, but it was lower compared to the initial visit. A decrease in the CAP was observed for Patient 2 (from stage S3 to stage S1). However, in both of these patients, their BMI z-scores were over 1.0, suggesting obesity (Patient 1) or overweight (Patient 2). In Patient 4, CAP correlated to no steatosis (Table 1, Fig. 1). Patient 3 did not show up for this visit and was consequently lost to follow-up.

Discussion

A fixed-dose combination of LDV/SOF is approved by the European Medicines Agency and Food and Drug Administration for the treatment of chronic HCV infection with genotypes 1, 4, 5, and 6 in children and adolescents 3 years of age and older [18–20]. Its safety and efficacy have been confirmed in phase II

and III clinical studies [18–20]. However, there are only limited data available on the LDV/SOF efficacy in children with significant fibrosis [9]. In addition, little is known about the long-term outcomes and the influence of the antiviral treatment on liver fibrosis. Patients with confirmed liver fibrosis should be closely monitored even after effective antiviral treatment of CHC [21]. Interestingly, there is evidence that in adult patients, liver fibrosis may be to some extent reversed by DAA treatment [21–24]. Bachofner et al. revealed a 32% reduction in LSM after DAA treatment in 392 adult patients with CHC complicated by fibrosis [25]. However, patients with significant fibrosis are still at risk of HCC development even after achieving SVR [21,26]. Mogahed et al. recently reported improvement in LSM in pediatric patients with CHC after treatment with DAA [10]. They studied 23 Egyptian children infected with HCV genotype 4 aged 10 to 18 years with variable degrees of fibrosis at baseline and found a significant improvement in LSM, APRI, and FIB-4 one year after SVR achievement. In 13 (56.5%) of their patients, the LSM improved; in seven patients, it was stationary; and the remaining three subjects showed a mild increase in LSM, with improvement in the APRI and FIB-4 [10]. This observation is consistent with the results of our study. In 2 out of 4 patients, a significant improvement and regression of liver fibrosis were revealed (from stage F4 and F2 to F0-F1 on the METAVIR scale) one year after the end of LDV/SOF therapy. In one patient, the LSM median increased 12 weeks after the end of the treatment and then decreased, but it still correlated to stage F4. In all these patients an improvement in the APRI was observed. Similar observations were reported by Makhlouf et al. in their 65 adolescents with CHC genotype 4 treated with LDV/SOF for 12 weeks [27]. At SVR12, they observed a significant improvement in liver stiffness measured by shear wave elastography and the APRI. In 14/65 (21/6%) patients, there was a transition in the stage of fibrosis observed: in 10 cases from F1 to F0, in three cases from F2 to F1, and in one case from F3 to F2 [27].

Factors that could influence the regression of liver fibrosis after successful DAA treatment remain unknown. In the study by Mogahed et al., comorbidities or previous ineffective treatment with interferon were not associated with increased LSM one year after SVR had been achieved [10]. Among our patients, the one subject in which the LSM increased after completing the LDV/SOF treatment was coinfected with HIV; he had been previously ineffectively treated with interferon with ribavirin and was older compared to patients who achieved regression of fibrosis.

The COVID-19 pandemic, which was announced in March 2020, has led to the disruption of the healthcare system and has had a significant negative impact on the care of patients with chronic diseases, including our therapeutic program for children with CHC. In March 2020, our department was transformed to a setting dedicated for COVID-19 patients. Consequently, all visits for non-COVID patients between March and July 2020 had to be cancelled or postponed. However, we have prepared and followed the new guidelines for management of children and adolescents with CHC during the COVID-19 pandemic [28]. Several efforts were made to prioritize patient care in our children with CHC. In the case of patients receiving DAA therapy, these efforts included using telemedicine for monitoring the patient's general condition, adherence to treatment, and the side effects of the therapy at least every four weeks; cooperating with general practitioners; using local laboratory testing for follow-up testing; and engaging

in the home delivery of DAAs [28]. All these efforts resulted in completing the full treatment regimen by all four patients. However, several monitoring visits were unfortunately cancelled. This problem in particular appeared in Patient 3, who was the last patient included in the therapeutic program (in February 2020). He completed his visit at 4 weeks of treatment, but the next monitoring visits were cancelled and replaced by phone calls every 4 weeks. Home delivery of LDV/SOF was arranged for him until the end of treatment. After 12 weeks of treatment his ALT and AST were tested in the local laboratory, which revealed further improvement in their levels (120 and 44 IU/L, compared to 438 and 184 IU/L at the start of treatment, and 272 and 111 IU/L after 4 weeks). The patient was asked to attend follow-up visits to assess the SVR and long-term outcome of treatment, but due to family and social problems and the long distance from our center, he refused to come and was lost to follow-up.

The main limitation of this study was the low number of patients included in the final analysis. However, to the best of our knowledge, there is only one report available on the long-term effects of DAA treatment in children including the influence of the therapy on liver fibrosis [10]. Therefore, it is worthwhile to share our unique data. In most pediatric cohorts, cirrhotic patients are underrepresented; thus, finding larger groups of these specific patients would be difficult. The second issue are the gaps in the available data due to the disruption caused by COVID-19 pandemic. However, it is worth noting, that DAA therapies are simple, short, and safe. Thus, even when close monitoring of patients is not possible, positive outcomes of treatment may be achieved.

Based on our experience, we conclude that treatment with a fixed-dose LDV/SOF in children with significant fibrosis in the course of CHC is safe and effective. A one-year observation of these patients after the end of treatment revealed that regression of liver fibrosis is possible but not obligatory. Further observations in larger groups of patients are necessary to find predictors of liver fibrosis regression in pediatric patients with CHC.

Table 1
Clinical and laboratory characteristics of four patients with chronic hepatitis C and significant fibrosis treated with ledipasvir/sofosbuvir

Feature		Patient 1	Patient 2	Patient 3	Patient 4
Sex		Female	Male	Male	Male
Age at start of the treatment (years)		12	16	17	15
HCV genotype		1b	4	1b	1b
Mode of HCV infection		Vertical	Vertical	Vertical	Vertical
Previous ineffective anti-HCV treatment (interferon plus ribavirin)		Yes	Yes	Yes	No
Duration of LDV/SOF treatment (weeks)		24	12	24	12
BMI (kg/m^2)/ BMI *z*-score	Start of LDV/SOF	25.4 / 2.07	25.7/ 1.55	37.0/ 3.28	20.4/ 0.23
	EOT	NA	27.2/ 1.46	NA	21.7/ 0.46
	Posttreatment week 12	27.9 / 2.33	27.5/ 1.49	NA	NA
	Posttreatment week 52	32.3 / 2.79	28.3/ 1.76	NA	24.4/ 0.97
ALT (IU/mL)	Start of LDV/SOF	40	52	438	46
	4 weeks	14	22	272	24
	EOT	NA	63	NA	20
	Posttreatment week 12	21	27	NA	NA
	Posttreatment week 52	21	22	NA	17
HCV viral load (IU/mL)	Start of LDV/SOF	2.23 x 10^6	4.89 x 10^5	7.0 x 10^4	6.28 x 10^5
	4 weeks	< 12	< 12	< 12	Undetectable
	EOT	NA	Undetectable	NA	Undetectable
	Posttreatment week 12	Undetectable	Undetectable	NA	NA

ALT – alanine aminotransferase; APRI - aspartate transaminase-to-platelet ratio index; BMI – body mass index; CAP - controlled attenuation parameter; EOT – end of treatment; FIB-4 – Fibrosis-4 index; LDV/SOF – ledipasvir/sofosbuvir; LSM – liver stiffness measurement; NA – not available; S – stage

Feature		Patient 1	Patient 2	Patient 3	Patient 4
	Posttreatment week 52	Undetectable	Undetectable	NA	Undetectable
LSM (median; kPa/METAVIR)	Start of LDV/SOF	12.5/F4	14/F4	13.4/F4	8.9/F2
	Posttreatment week 12	6.8/F0-F1	33.6/F4	NA	NA
	Posttreatment week 52	6.2/F0-F1	25.9/F4	NA	6.1/F0-F1
CAP (dB/m)/S	Start of LDV/SOF	253/S1	235/S0	253/S1	191/S0
	Posttreatment week 12	197/S0	298/S3	NA	NA
	Posttreatment week 52	240/S1	248/S1	NA	225/S0
APRI	Start of LDV/SOF	0.536	0.615	2.359	0.366
	Posttreatment week 12	0.288	0.382	NA	NA
	Posttreatment week 52	0.230	0.347	NA	0.229
FIB-4	Start of LDV/SOF	0.407	0.546	0.766	0.324
	Posttreatment week 12	0.326	0.499	NA	NA
	Posttreatment week 52	0.261	0.532	NA	0.356

ALT – alanine aminotransferase; APRI - aspartate transaminase-to-platelet ratio index; BMI – body mass index; CAP - controlled attenuation parameter; EOT – end of treatment; FIB-4 – Fibrosis-4 index; LDV/SOF – ledipasvir/sofosbuvir; LSM – liver stiffness measurement; NA – not available; S – stage of steatosis

Declarations

Acknowledgements

Not applicable.

Authors' contributions

MPŚ performed the research, designed the research study, collected and analyzed the data, contributed to the interpretation of the data, and drafted the manuscript; AD collected and analyzed the data; MM contributed to the study design and critically revised the manuscript; all authors read and approved the final manuscript

Competing interests

The authors declare that they have no competing interests.

Funding

The therapeutic program was available courtesy of the donation of LDV/SOF by the pharmaceutical company (Gilead Sciences Poland Sp. z o.o.). The pharmaceutical company did not have any role in performing the study, nor in writing or approving this manuscript.

Availability of data and material

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

References

1 Bortolotti, F. *et al.* Long-term course of chronic hepatitis C in children: from viral clearance to end-stage liver disease. *Gastroenterology* **134**, 1900-1907, doi:10.1053/j.gastro.2008.02.082 [doi] (2008).

2 European Paediatric Hepatitis, C. V. N. Three broad modalities in the natural history of vertically acquired hepatitis C virus infection. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* **41**, 45-51, doi:CID35334 [pii] (2005).

3 Jara, P. *et al.* Chronic hepatitis C virus infection in childhood: clinical patterns and evolution in 224 white children. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* **36**, 275-280, doi:CID21154 [pii] (2003).

4 Pokorska-Śpiewak, M. *et al.* Determinants of liver disease progression in children with chronic hepatitis C virus infection. *Pol J Pathol* **66**, 368-375 (2015).

5 Guido, M. *et al.* Fibrosis in chronic hepatitis C acquired in infancy: is it only a matter of time? *The American Journal of Gastroenterology* **98**, 660-663, doi:S000292700206015X [pii] (2003).

6 Pokorska-Śpiewak, M. *et al.* Liver Fibrosis Evaluated With Transient Elastography in 35 Children With Chronic Hepatitis C Virus Infection. *Pediatr Infect Dis J* **40**, 103-108, doi:10.1097/INF.0000000000002913 (2021).

7 Turkova, A. *et al.* Advanced liver disease in Russian children and adolescents with chronic hepatitis C. *J Viral Hepat* **26**, 881-892, doi:10.1111/jvh.13093 (2019).

8 Modin, L. *et al.* Epidemiology and natural history of hepatitis C virus infection among children and young people. *J Hepatol* **70**, 371-378, doi:10.1016/j.jhep.2018.11.013 (2019).

9 Indolfi, G. *et al.* Systematic review with meta-analysis: the efficacy and safety of direct-acting antivirals in children and adolescents with chronic hepatitis C virus infection. *Aliment Pharmacol Ther* **52**, 1125-1133, doi:10.1111/apt.16037 (2020).

10 Mogahed, E. A. *et al.* Improvement in Liver Stiffness in Pediatric Patients with Hepatitis C Virus after Treatment with Direct Acting Antivirals. *J Pediatr* **233**, 126-131, doi:10.1016/j.jpeds.2021.02.012 (2021).

11 Indolfi, G. *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* **66**, 505-515, doi:10.1097/MPG.0000000000001872 (2018).

12 Zeng, J. *et al.* Feasibility study and reference values of FibroScan 502 with M probe in healthy preschool children aged 5 years. *BMC Pediatr* **19**, 129, doi:10.1186/s12887-019-1487-6 (2019).

13 Castera, L. *et al.* Prospective comparison of transient elastography, Fibrotest, APRI, and liver biopsy for the assessment of fibrosis in chronic hepatitis C. *Gastroenterology* **128**, 343-350, doi:S0016508504020293 [pii] (2005).

14 Sasso, M., Miette, V., Sandrin, L. & Beaugrand, M. The controlled attenuation parameter (CAP): a novel tool for the non-invasive evaluation of steatosis using Fibroscan. *Clin Res Hepatol Gastroenterol* **36**, 13-20, doi:10.1016/j.clinre.2011.08.001 (2012).

15 Sterling, R. K. *et al.* Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. *Hepatology (Baltimore, Md.)* **43**, 1317-1325, doi:10.1002/hep.21178 (2006).

16 Wai, C. T. *et al.* A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology* **38**, 518-526, doi:10.1053/jhep.2003.50346 (2003).

17 Lin, Z. H. *et al.* Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: an updated meta-analysis. *Hepatology (Baltimore, Md.)* **53**, 726-736, doi:10.1002/hep.24105 [doi] (2011).

18 Balistreri, W. F. *et al.* The safety and effectiveness of ledipasvir-sofosbuvir in adolescents 12-17 years old with hepatitis C virus genotype 1 infection. *Hepatology* **66**, 371-378, doi:10.1002/hep.28995 (2017).

19 Schwarz, K. B. *et al.* Ledipasvir-Sofosbuvir for 12 Weeks in Children 3 to <6 Years Old With Chronic Hepatitis C. *Hepatology* **71**, 422-430, doi:10.1002/hep.30830 (2020).

20 Murray, K. F. *et al.* Safety and Efficacy of Ledipasvir-Sofosbuvir With or Without Ribavirin for Chronic Hepatitis C in Children Ages 6-11. *Hepatology* **68**, 2158-2166, doi:10.1002/hep.30123 (2018).

21 Rogers, M. E. & Balistreri, W. F. Cascade of care for children and adolescents with chronic hepatitis C. *World J Gastroenterol* **27**, 1117-1131, doi:10.3748/wjg.v27.i12.1117 (2021).

22 Chen, S. H. *et al.* Changes in liver stiffness measurement using acoustic radiation force impulse elastography after antiviral therapy in patients with chronic hepatitis C. *PLoS One* **13**, e0190455, doi:10.1371/journal.pone.0190455 (2018).

23 Rockey, D. C. Fibrosis reversal after hepatitis C virus elimination. *Curr Opin Gastroenterol* **35**, 137-144, doi:10.1097/MOG.0000000000000524 (2019).

24 Knop, V. *et al.* Regression of fibrosis and portal hypertension in HCV-associated cirrhosis and sustained virologic response after interferon-free antiviral therapy. *J Viral Hepat* **23**, 994-1002, doi:10.1111/jvh.12578 (2016).

25 Bachofner, J. A. *et al.* Direct antiviral agent treatment of chronic hepatitis C results in rapid regression of transient elastography and fibrosis markers fibrosis-4 score and aspartate aminotransferase-platelet ratio index. *Liver Int* **37**, 369-376, doi:10.1111/liv.13256 (2017).

26 Chan, P. P. Y., Levy, M. T., Shackel, N., Davison, S. A. & Prakoso, E. Hepatocellular carcinoma incidence post direct-acting antivirals in hepatitis C-related advanced fibrosis/cirrhosis patients in Australia. *Hepatobiliary Pancreat Dis Int* **19**, 541-546, doi:10.1016/j.hbpd.2020.06.013 (2020).

27 Makhlouf, N. A. *et al.* Ledipasvir/Sofosbuvir in Adolescents With Chronic Hepatitis C Genotype 4 With and Without Hematological Disorders: Virological Efficacy and Impact on Liver Stiffness. *J Pediatric Infect Dis Soc* **10**, 7-13, doi:10.1093/jpids/piaa006 (2021).

28 Pokorska-Śpiewak, M. & Śpiewak, M. Management of hepatitis C in children and adolescents during COVID-19 pandemic. *World J Hepatol* **12**, 485-492, doi:10.4254/wjh.v12.i8.485 (2020).

Figures

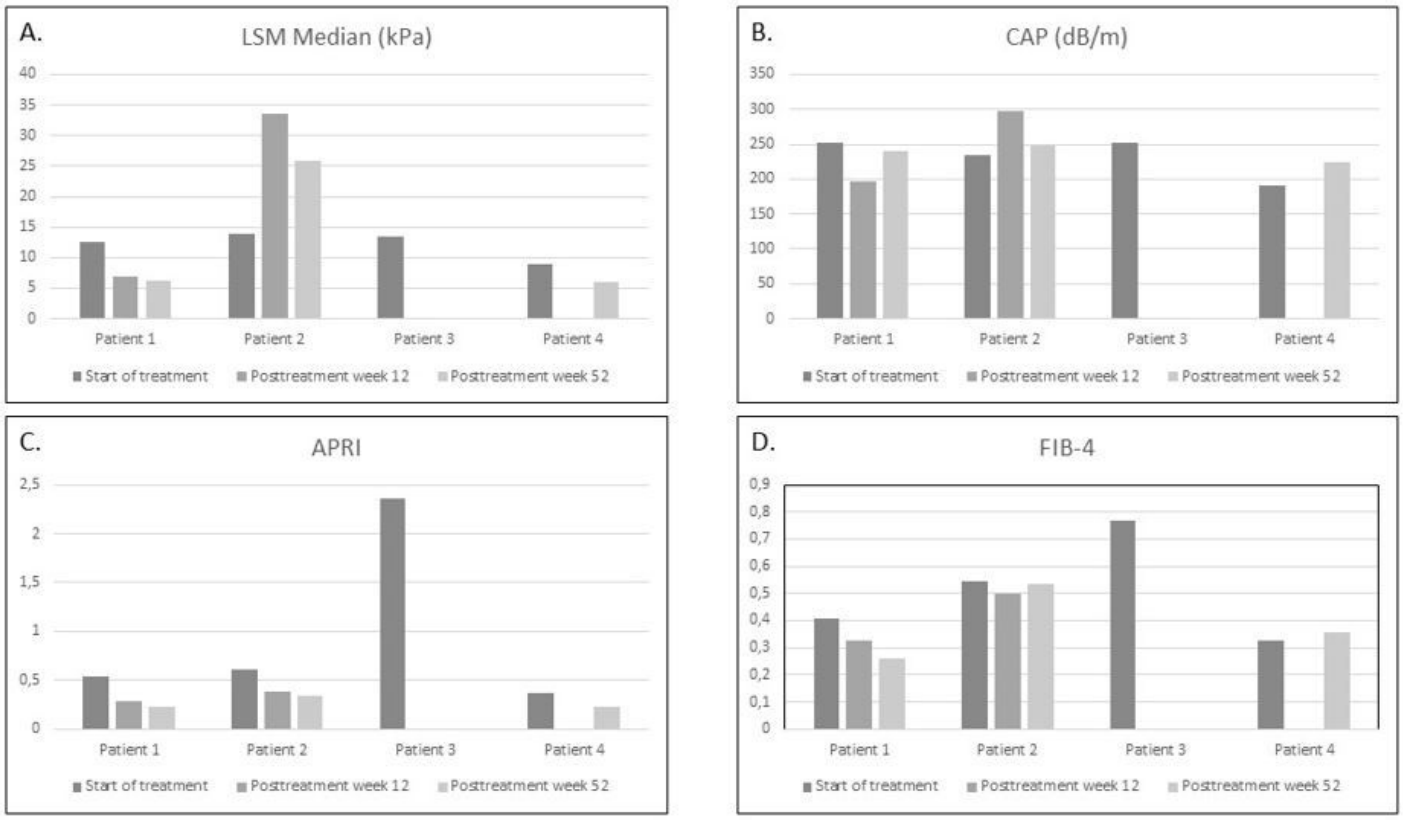

Figure 1

Noninvasive evaluation of liver fibrosis and steatosis in four patients treated with ledipasvir/sofosbuvir at the start of treatment, at week 12, and week 52 posttreatment. A. Liver stiffness measurement (LSM) median B. Controlled attenuation parameter (CAP) C. Aspartate transaminase-to-platelet ratio index (APRI) D. Fibrosis-4 index (FIB-4)