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Original paper

Changes in liver stiffness and steatosis in children after successful treatment with sofosbuvir/velpatasvir: Results of the PANDAA-PED study

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Abstract

Aim of the study: The aim of this study was to analyze changes in liver stiffness and steatosis using noninvasive methods in children aged 6 to 18 years up to one year after successful treatment with sofosbuvir/velpatasvir (SOF/VEL).

Material and methods: Evaluation of liver stiffness and steatosis was performed in 49 patients at 12 weeks and one year after treatment using noninvasive methods. Liver stiffness measurement (LSM) and the controlled attenuation parameter (CAP) were obtained by transient elastography (FibroScan 530, Echosens).

Results: At baseline, LSM corresponded to a METAVIR F score of 0/1 in 48/49 (98%) participants. There was a decrease in mean LSM values from baseline to posttreatment visits (from 4.63 kPa to 4.26 kPa at 12 weeks, and 4.15 kPa at one year after treatment). In one girl who presented with significant fibrosis (LSM 11.3 kPa, F3) before the treatment, regression of stiffness was observed to 7.6 kPa (F2) at 12 weeks after treatment and 5.4 kPa (F0/1) at one year after treatment. There was an increase in the mean CAP value of +12.44 dB/m at 12 weeks after treatment compared to baseline, but the difference at one year after treatment was insignificant. A correlation between higher CAP values and older participants' age was observed at all the visits. Children with body mass index (BMI) z-score values > 1.0 presented with higher CAP values both before and after treatment.

Conclusions: Most children with chronic hepatitis C present with normal liver stiffness. However, its regression may occur to some extent after successful treatment with SOF/VEL. A transient increase in hepatic steatosis was observed after eradication of HCV, which requires further investigation.

Key words: liver fibrosis, liver stiffness, steatosis, hepatitis C, sofosbuvir/velpatasvir.

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Introduction

It has been estimated that approximately 3.25 million children under 18 years live with active hepatitis C virus (HCV) infection globally [1]. Considering the natural history of the disease, 25% to 40% of children infected vertically with HCV, spontaneously clear the infection during the first 4 to 7 years of life, whereas the remainder will develop chronic infection, which tends to have a milder course compared to adults [2]. However, according to the more recent data, cirrhosis may occur in one third of patients infected during childhood, a median of 33 years after infection, irrespective of the route of the infection [3]. In addition, there is a risk of advanced fibrosis (F4 in METAVIR

scale) in adolescents with chronic hepatitis C that ranges from 2% to 9% [4].

Novel direct-acting antiviral (DAA) therapies have revolutionized the HCV treatment in both adult and pediatric patients. They are now recommended by the World Health Organization (WHO) for the treatment of chronic hepatitis C in children aged at least 3 years of age [5]. Early detection of HCV infection in children and adolescents seems crucial to prevent disease progression and its long-term consequences [6]. Identifying patients at an early stage of disease allows for timely treatment intervention, which should reduce the risk of advanced liver disease development [6]. However, due to the lower burden of infection, lack of national policies on hepatitis C management, and only recently approved DAA therapies for children, there has been much less attention to addressing HCV in children and adolescents [7]. Thus, there are still gaps in our knowledge concerning effects of DAA treatment in pediatric patients. In particular, evaluation of the longer influence of the successful DAA therapy on the liver stiffness parameters requires further studies.

The pangenotypic regimen of sofosbuvir/velpatasvir (SOF/VEL) was demonstrated to be highly effective and safe in treating children aged 3-17 years with chronic HCV infection [8]. In addition, recently 100% efficacy and a good safety profile of a SOF/VEL combination were reported in 50 patients aged 6 to 18 years treated in the PANDAA-PED study ('Treatment of chronic hepatitis C in children aged 6-18 years using a pangenotypic direct-acting antiviral sofosbuvir/velpatasvir') [9]. In the current part of the study, we aimed to analyze changes in liver stiffness and steatosis using noninvasive methods up to one year after successful treatment with SOF/VEL.

Material and methods

Study design

The PANDAA-PED study is a noncommercial, nonrandomized, open-label study funded by the Medical Research Agency, Warsaw, Poland (grant number 2019/ABM/01/00014). Fifty children aged 6-18 years were successfully treated for HCV infection between January, 2022 and October, 2022 using a 12-week course of fixed-dose SOF/VEL adjusted to the body weight [9]. The primary endpoints of this study included evaluation of the SOF/VEL efficacy (defined as sustained virologic response, SVR12, with undetectable HCV RNA at 12 weeks after treatment) and safety in children aged 6 to 18 years. Among secondary endpoints, there was an analysis of the long-term influence of the treatment on liver disease parameters, including liver stiffness and steatosis. In this part of the study, we analyzed the results of the following visits: at baseline (before the treatment), at 12 weeks after treatment, and at one year after treatment. All the visits in this study were completed by October 31, 2023. The analysis included only those children who underwent all the scheduled appointments.

Evaluation of liver stiffness and steatosis

Evaluation of liver stiffness and steatosis was performed at all three visits by the transient elastography (TE) method by certified trained examiners using a FibroScan 530 device (M probe) (Echosens, Paris, France). The liver stiffness measurement (LSM) and controlled attenuation parameter (CAP) were simultaneously obtained. The final LSM result was expressed in kilopascals (kPa), and it was the median value of at least 10 valid measurements. It corresponded to liver fibrosis on the METAVIR scale according to the Castera TE cutoffs as follows: no to mild fibrosis (F0/1), 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 [10]. 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 interpreted 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) [11, 12].

In addition to the TE, which was considered as a reference method of liver stiffness and steatosis assessment for this study, simultaneously we performed a biomarker evaluation. Two indirect fibrosis biomarkers were calculated, the aspartate transaminase-to-platelet ratio index (APRI) and fibrosis-4 index (FIB-4), according to the published analytic recommendations [13, 14]:

$$APRI = [(AST\ (IU/l)/AST\ ULN)/Platelet\ count\ (10^9/l)] \times 100$$

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

The upper limits of normal (ULN) for alanine and aspartate aminotransferases (ALT and AST) were set at 40 IU/l. The following cutoffs were considered to indicate significant fibrosis: APRI > 0.7 and FIB-4 > 1.45 [13, 15]. The selection of the cutoffs for APRI and FIB-4 was based on adult studies, as they have not been validated in children and adolescents.

Statistical analysis

Categorical variables were expressed as numbers (percentages of total) and they were compared using a chi square test. Continuous data were tested for normal distribution using the Kolmogorov-Smirnov test and were presented as means (95% confidence intervals [CI]) or medians with interquartile ranges (IQR). To compare the parameters between the successive visits, Student's *t*-test was used. To analyze correlations between different non-invasive biomarkers, Spearman's rho correlation coefficient with 95% CI was calculated. A two-sided p value of < 0.05 was considered to indicate significance. Statistical analyses were performed using MedCalc Statistical Software version 22.018 (MedCalc, Ostend, Belgium).

Ethical statement

We collected written informed consent from all the patients and/or their parents/guardians before their inclusion in the study. The local ethics committee of the Medical University of Warsaw approved this study (approval number KB/136/2020, September 14, 2020 and KB/30/A2021, April 19, 2021). The investigation was performed in accordance with the ethical standards in the 1964 Declaration of Helsinki and its later amendments.

Results

Study participants

Characteristics of the study group at baseline and at one year after treatment are presented in Table 1. Among 50 successfully treated children, 49 participants (23 boys and 26 girls) completed all the visits and were included in the current analysis. One 11-year old girl with normal LSM and CAP at baseline was lost to follow-up after the 12-week posttreatment visit. All children remained HCV RNA-negative at the last visit.

Noninvasive evaluation of liver fibrosis and steatosis

LSM

At baseline, LSM corresponded to a METAVIR F score of 0/1 in 48/49 (98%) participants. In one 13-year old girl who presented with significant fibrosis (LSM 11.3 kPa, F3 on METAVIR scale) before the treatment, regression of liver stiffness was observed to 7.6 kPa (F2) at 12 weeks after treatment and 5.4 kPa (F0/1) at one year after treatment. All the LSM values among the remaining participants were within ranges corresponding to F0/1. There was a decrease in mean LSM values observed from baseline to posttreatment visits (-0.37 kPa and -0.48 kPa at 12 weeks and one year after treatment, respectively; Table 2). When we excluded the patient with baseline LSM of 11.3 kPa from the analysis, LSM values were lower than the baseline value of 4.49 (4.21; 4.77) kPa at both 12 weeks and one year after treatment by a mean difference of –0.29 ±1.13 kPa, $p = 0.08$, and –0.36 ±1.13, $p = 0.07$, respectively.

Participants' age was not correlated with LSM values at baseline, but higher LSM values were observed in older children at 3 and 12 months after the treatment ($p = 0.06$, $p = 0.05$, respectively) (Table 2).

CAP

Two participants presented with CAP > 238 dB/m indicating steatosis at baseline. This number increased

Table 1. Characteristics of the study group at baseline and at one year after the end of treatment with sofosbuvir/velpatasvir (for 49 patients who completed all the scheduled visits)

Characteristic	Baseline (before treatment)	One year after treatment
Sex (male/female), *n* (%)	23 (47)/26 (53)	
Age (years), mean ±SD	9.9 ±2.5	10.9 ±2.5
Mother-to-child HCV transmission, *n* (%)	46 (94)	
HCV genotype, *n* (%)	1a – 3 (6) 1b – 33 (67) 3 – 10 (21) 4 – 3 (6)	
BMI z-score, mean ±SD	0.39 ±1.29	0.29 ±1.19
BMI z-score ⩾ 1 SD (overweight/obese)*, *n* (%)	16 (33)	17 (35)
Alanine aminotransferase (IU/ml), median (IQR)	49 (29; 71)	18 (15; 21)
Aspartate aminotransferase (IU/ml), median (IQR)	46 (38; 59)	29 (24; 33)
Total bilirubin (µmol/l), median (IQR)	9.3 (6.6; 11.8)	9.6 (7.6; 12.5)
Hemoglobin (g/dl), mean ±SD	13.49 ±0.82	13.08 ±0.87
Platelets (G/l), mean ±SD	325 ±71	291 ±55
HCV RNA PCR log10 (IU/ml), median (IQR)	5.81 (5.35; 6.24)	Undetectable in all cases
Anti-HCV positive, *n* (%)	49 (100)	48 (98)

IQR – interquartile range
** According to the WHO Growth reference data (https://www.who.int/tools/growth-reference-data-for-5to19-years).*

Table 2. Liver stiffness measurement (LSM) at baseline, 3 months after the end of treatment, and 12 months after the end of treatment

Parameter	Baseline	3 months after treatment	12 months after treatment
LSM (kPa), mean (95% CI)	4.63 (4.23-5.02)	4.26 (3.98-4.55)	4.15 (3.87-4.43)
Change in LSM compared to baseline, mean (SD) *p* value	–	−0.37 (±1.22) 0.03	−0.48 (±1.56) 0.03
Children with LSM > 7.0 kPa, *n* (%)	1 (2)	1 (2)	0
LSM in a patient with baseline LSM > 7.0 kPa (kPa)	11.3	7.6	5.4
Correlation between LSM and patients' age, Spearman's rho correlation coefficient (95% CI) *p* value	0.11 (–0.17-0.51) 0.44	0.26 (–0.01-0.51) 0.06	0.27 (0.0-0.51) 0.05

CI – confidence interval, LSM – liver stiffness measurement

Table 3. Controlled attenuation parameter (CAP) at baseline, 3 months after the end of treatment, and 12 months after the end of treatment

Parameter	Baseline	3 months after treatment	12 months after treatment
CAP (dB/m), mean (95% CI)	180.73 (168.7-192.79)	193.06 (181.7-204.3)	190.6 (179.2-201.9)
Change in CAP compared to baseline, mean (SD) *p*-value	–	+12.44 (±38.42) 0.02	+9.86 (±41.94) 0.10
Children with CAP>238 dB/m, *n* (%)	2 (4)	4 (8)	4 (8)
Correlation between CAP and patients' age, Spearman's rho correlation coefficient (95% CI) *p* value	0.58 (0.38-0.74) < 0.0001	0.34 (0.06-0.57) 0.01	0.41 (0.15-0.62) 0.003

CAP – controlled attenuation parameter, CI – confidence interval

to 4 both at 12 weeks and one year after the treatment. In addition, there was an increase in the mean CAP value of +12.44 dB/m observed at 12 weeks after treatment compared to baseline ($p = 0.02$), but the difference was not significant at one year after treatment (+9.86 dB/m, $p = 0.1$; Table 3). There was a correlation between higher CAP values and older participants' age at all the visits (Table 3). In addition, children with BMI z-score values > 1.0 (corresponding to overweight/obesity) presented with higher CAP values at baseline (median of 202.5 dB/m vs. 163 dB/m, $p = 0.01$), at 12 weeks after treatment (208 dB/m vs. 187 dB/m, $p = 0.001$) and at one year after treatment (229 dB/m vs. 176.5 dB/m, $p = 0.0001$). No influence of HCV genotype (3 vs. others) on the CAP value was found at any of the visits.

Comparison between TE and serum biomarkers (APRI and FIB-4) evaluation

At baseline, 4 (8%) of children presented with APRI > 0.7, suggesting significant fibrosis, and the mean APRI values decreased after the treatment (Table 4). All FIB-4 values both before and after treatment were below 1.45, suggesting the absence of significant fibrosis; however, their means increased after the treatment within the normal ranges (Table 4). There was a significant correlation between APRI and FIB-4 at all the visits (Table 5).

There was no correlation between LSM and APRI at baseline and 12 weeks after treatment, and a negative correlation was found at one year after treatment (Table 5). LSM correlated with FIB-4 at 12 weeks after treatment but no correlation was found for the remaining two visits. In particular, in the girl presenting with significant fibrosis at baseline, all APRI values were < 0.7 and all FIB-4 evaluations were < 1.45, not indicating significant fibrosis at baseline or a decrease at the subsequent visits.

Discussion

No studies have analyzed liver disease parameters after successful SOF/VEL treatment in pediatric patients. Children with chronic hepatitis C usually present with no or only mild liver disease, including liver fibrosis; thus, available data on the possible regression of liver stiffness after DAA treatment and evaluation of the long-term outcomes of the therapy are lacking.

In the PANDAA-PED study, we treated successfully 50 children aged 6 to 18 years with SOF/VEL. All but one participant of this study had no fibrosis when evaluated using TE, which indicates no disease progression in this group of HCV-infected children. In none of

Table 4. Serum biomarkers in 49 pediatric patients treated with sofosbuvir/velpatasvir: at baseline, 3 months after the end of treatment, and 12 months after the end of treatment

Parameter	Baseline (0)	3 months after treatment (1)	12 months after treatment (2)	*p* (0 vs. 1)	*p* (0 vs. 2)
APRI	0.39 (0.34-0.44)	0.25 (0.23-0.27)	0.25 (0.23-0.27)	< 0.0001	< 0.0001
APRI > 0.7	4 (8)	0	1 (2)	0.04	0.17
FIB-4	0.21 (0.19-0.24)	0.23 (0.21-0.26)	0.25 (0.23-0.28)	0.1	< 0.0001
FIB-4 > 1.45	0	0	0	–	–

Data are presented as means (95% confidence intervals) and numbers (%) of patients presenting with elevated values of subsequent markers
APRI – AST to platelet ratio index, FIB-4 – fibrosis-4

Table 5. Correlations between different methods of non-invasive assessment of liver fibrosis at baseline, 3 months after the end of treatment, and 12 months after the end of treatment

Comparison	Baseline	3 months after treatment	12 months after treatment
APRI vs. FIB-4	0.33 (0.05-0.56) *p* = 0.01	0.36 (0.08-0.58) *p* = 0.01	0.48 (0.23-0.68) *p* = 0.0004
LSM vs. APRI	–0.03 (–0.31-0.24) *p* = 0.81	–0.05 (–0.33-0.22) *p* = 0.69	–0.36 (–0.55 - –0.03) *p* = 0.02
LSM vs. FIB-4	0.09 (–0.19-0.36) *p* = 0.52	0.32 (0.04-0.55) *p* = 0.02	(–0.26-0.30) *p* = 0.89

Data are presented as Spearman's rho correlation coefficient (95% CI), p value
APRI – AST to platelet ratio index, FIB-4 – fibrosis-4, LSM – liver stiffness measurement

these children was any progression in LSM observed up to one year after treatment. In the girl presenting with significant (F3) fibrosis at baseline, regression in LSM was revealed to F0/1 at one year after treatment. Similar observations on the SOF/VEL treatment outcomes are lacking, but there is some evidence available from the studies on another combination, SOF/ledipasvir (SOF/LDV) in adolescents (10-18 years) infected with HCV genotype 1 and 4 [11, 16-18]. In the largest study, by Fahmy et al., analyzing 85 patients with a median baseline LSM of 5.8 kPa, and a follow-up LSM (12 months after HCV eradication) of 5.1 kPa ($p = 0.045$), 62 (73%) participants presented with more than a 30% decrease in LSM: 16 (19%) experienced regression, and 46 (54%) non-progression of LSM [17]. Of 18 patients with significant baseline fibrosis (≥ F2 on a 6-point Ishak score), 13 regressed to F0/1, 2 from F6 to F5, 1 was unchanged at F3, and 2 increased to F5 and F6. In another Egyptian study by Mogahed *et al.*, on 23 cases aged 10 to 18 years with variable degrees of fibrosis at baseline, a significant improvement in LSM, APRI, and FIB-4 was observed. In 13 patients (56.5%), LSM improved, in 7 it was unchanged, and in the remaining 3 patients there was a mild increase in LSM [11]. This is concordant with our previous observations on patients after successful treatment with SOF/LDV, among whom all patients with LSM corresponding to F0/1 remained stable, and among 4 patients with significant fibrosis, an improvement (from F4 and F2 to F0/1) was observed in two cases one year after treatment, in one participant LSM increased at 12 weeks after treatment and then decreased at one-year observation, but remained correlated with stage F4 [16]. The results of these studies confirm that after successful treatment with SOF-based therapies, regression of liver stiffness may be possible even from F4 to F0/1, but it is not certain [11, 16-18]. However, predictors of regression remain unknown. One possible explanation for non-regression is the presence of comorbidities (e.g., HIV coinfection, thalassemia, steatosis) [11, 16, 17].

It should be highlighted that causes of elevated LSM other than liver fibrosis are possible, including liver inflammation (elevated ALT and AST) or heart congestion (unlikely in our cohort). Thus, the improvement in LSM may also be the consequence of improvement in inflammation due to HCV eradication, and not only reflect the regression in liver fibrosis. On the other hand, it is not possible to perform liver biopsy in children after successful eradication of HCV, and thus to distinguish between the possible causes of LSM regression.

Another finding of this study, which has not been reported in pediatric patients so far, was the transient increase in hepatic steatosis (CAP) after treatment with SOF/VEL. The proportion of children presenting with steatosis at baseline was low. However, we observed an increase in the number of children pre-

senting with elevated CAP after the therapy. In addition, there was an increase in the mean CAP value of +12.44 dB/m at 12 weeks after treatment compared to baseline, but the difference at one year after treatment (+9.86 dB/m) was not significant, suggesting that the increase was transient. Similar observations were made in adult studies on the influence of DAA treatment on CAP values [19, 20]. Rout *et al.* analyzed the LSM and CAP at one year after treatment in a cohort of 372 patients with a mean age of 38.1 years, and found that CAP increased from baseline of 210 dB/m to 234 dB/m, with a median increase of 25 dB/m ($p < 0.001$) [20]. In their group, low baseline CAP and low albumin level were significantly associated with the CAP increase. Another adult study on 280 patients who achieved SVR12 revealed that after viral eradication, an increase in hepatic steatosis may occur [19]. At SVR12 evaluation, 66.4% of their participants had a CAP score ≥ 248 dB/m, which indicated an increase of 4.6% compared to baseline. In addition, they observed a significant increase in triglyceride levels, cholesterol levels, and body mass index at SVR12 evaluation compared to the baseline [19]. Thus, excessive calorie intake might be responsible for the observed increase in liver steatosis. Other adult studies suggested an increasing effect of DAAs on elevated triglycerides and cholesterol levels [21-23]. This observation requires further evaluation in children and adolescents. However, in our study, CAP positively correlated with children's BMI z-score, which may suggest a role of metabolic factors in progression of liver steatosis.

Another issue analyzed in this study was the comparison between TE results and evaluation of serum biomarkers. Noninvasive methods have replaced liver biopsy for the evaluation of liver fibrosis in children with chronic hepatitis C; however, they have not been adequately validated in pediatric patients. Available data suggest that TE accurately discriminates between patients with and without significant fibrosis; thus, this method was used as a reference in this study [24-26]. In our cohort, there was a poor correlation between LSM values vs. APRI and FIB-4. This is in contrast to our previous findings on adolescents with chronic hepatitis C, where a good correlation between these methods for the staging of liver fibrosis was revealed, but suggesting lower cut-offs for APRI and FIB-4 compared to adults [4]. The discrepancy between TE and serum biomarkers in the current study may be explained by a significant predominance of children with normal (low) LSM in this cohort. In fact, APRI and FIB-4 should distinguish patients with significant fibrosis from those with normal liver stiffness. Thus, low values of APRI and FIB-4 correlated with F0/1 in most cases. However, they were ineffective in predicting significant fibrosis in the only participant presenting with stage F3. This issue requires further analysis in larger groups of patients with advanced liver fibrosis.

To the best of our knowledge, we present the first cohort of children at one year after successful eradication of HCV using SOF/VEL. In addition, compared to other studies on the outcomes of SOF-based therapies, we analyzed not only adolescents, but also children as young as 6 years of age. However, our study has some limitations. Firstly, our study group was small, but large studies in this field in children are unavailable and this is one of the two studies analyzing the effects of SOF/VEL in children [8, 9]. Secondly, most children in our cohort presented without liver fibrosis at baseline, which precluded analysis of the influence of treatment on significant fibrosis. In addition, the PANDAA-PED study protocol did not include evaluation of metabolic factors (e.g., lipid levels) and their influence on CAP.

In conclusion, the results of the PANDAA-PED study showed that most children aged 6 to 18 years with chronic hepatitis C present with normal liver stiffness; however, its regression may occur to some extent after successful treatment with SOF/VEL. A transient increase in hepatic steatosis may be observed after eradication of HCV, which requires further investigation in pediatric patients after DAA treatment.

Disclosures

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The study was approved by the Bioethics Committee of the Medical University of Warsaw (Approval No. KB/136/2020, September 14, 2020 and KB/30/A2021, April 19, 2021).

The authors declare no conflict of interest.

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