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Effects of Dual Sofosbuvir/Daclatasvir Therapy on Weight and Linear Growth in Adolescent Patients With Chronic Hepatitis C Virus Infection

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Abbreviated title: Effects of Sofosbuvir/Daclatasvir Therapy on Growth Indices.

Running head: Does SOF/DCV Therapy Affect Growth in Adolescents?

The study protocol was reviewed and approved by the Research Ethics Committee of Faculty of Medicine, Alexandria University (IRB00007555) according to the Declaration of Helsinki. All

subjects and their parents/guardians gave written informed consent before any treatment interventions were performed.

Disclosures of Conflict of Interest: Mostafa Yakoot and Alaa M Abdo have conducted clinical trials on Pharco products, Sherine Helmy works and holds stocks in Pharco Corporation; all others have nothing to disclose.

AUTHORSHIP

***Author contributions*:** Mostafa Yakoot, Mortada El-Shabrawi, and Sherine Helmy designed the concept of study. Mostafa Yakoot, Mortada El-Shabrawi, Manal M AbdElgawad, Aml A Mahfouz, Ahmed Khalil Alaa M Abdo, Naglaa M Kamal, Enas Kamal and Hisham El-Khayat recruited the patients, conducted the study procedures and collected the data. Mostafa Yakoot interpreted the data and wrote the first draft of the manuscript. All authors reviewed the manuscript and approved the final version to be published.

ABSTRACT

Negative effects on growth indices had been reported in children treated with interferon for chronic viral hepatitis. Forty chronic HCV infected adolescents, 12 to 17 years of age were treated with sofosbuvir/daclatasvir therapy for 12 weeks. The intent-to-treat (ITT) sustained virologic response rate at 12 weeks after end of treatment (SVR12) was 39/40 (97.5%). Unlike interferon-based-therapy, we did not detect significant negative effects on linear growth or weight. Contrarily, a trend to increased appetite and insignificant weight gain were observed but further larger studies are needed to confirm.

Key Words: Chronic hepatitis C, adolescents, sofosbuvir, daclatasvir, linear growth, weight.

INTRODUCTION

The directly-acting antiviral drugs (DAAs) have revolutionized the treatment for chronic hepatitis C virus (HCV) infection with higher cure rates, shorter courses of therapy and higher safety and tolerability than the previous interferon-based standard of care.[1-4]

Interferon-based therapy was known to be associated with many adverse effects in children as the case in adults. Peculiar to the growing pediatric age groups, there have been multiple reports of negative effects on linear growth, weight gain and other growth indices in children treated with interferon for chronic hepatitis C or B. [5-8] However, the effect of treatment with the new class of DAAs on growth indices in pediatric age groups has not been well evaluated.

Here we aimed to assess the short term effects of dual sofosbuvir/daclatasvir (SOF/DCV) therapy on linear growth and weight curves of chronic HCV infected adolescents during treatment till the end of 12 weeks post-treatment follow up period.

PATIENTS AND METHODS

This study is an extension of our previous cohort study published earlier. [9]

The study protocol had been reviewed and approved by the Research Ethics Committee of Faculty of Medicine, Alexandria University (IRB00007555) according to the Declaration of Helsinki. All subjects and their parents/guardians signed the informed consents before the start of the study interventions.

Procedures:

Starting from February 21, 2017, adolescent patients presenting, with chronic HCV infection, to 2 outpatient clinics in Alexandria and 2 in Cairo, Egypt were subjected to full screening for eligibility criteria. The results of the first 30 consecutively included patients who fulfilled the eligibility criteria and received the treatment were presented in the previously published study

report.[9] Here, we present the results of the total of 40 included patients under the same protocol with focused analysis on growth indices and virologic response as the primary endpoints.

During the screening / baseline visits (week 0) and all other study visits (week 2, Week 4, Week 12 (End of Treatment (EOT) and Week 24 (12 weeks after EOT), all patients were subjected to full physical examination and investigations as described in the previous report.[9]

The body weight was measured by an electronic digital scale accurate to 0.1 kg and the standing height was measured by Stadiometer to the nearest 0.1 cm. Anthropometric measurements were made during visits by a single observer at each study site. The serum HCV-RNA level (virus load) was tested using the Polymerase Chain Reaction (PCR) quantitative measurements by COBAS Amplicor 2.0, Roche Molecular Diagnostics, Pleasanton, CA, USA (lower limit of detection of 10 IU/mL).

All patients were subjected to dual SOF/DCV treatment (generic products produced by European Egyptian Pharmaceutical Industries, Alexandria, Egypt), with the same protocol as described in the previously published study for 12 weeks duration.

Outcome measures:

The primary outcome in this study included the comparison of means of repeated measures of weight-for-age z scores (ZWTAGE) and height-for-age z scores (ZHTAGE) from baseline values (first point) through the end of treatment (EOT: second point) till 12 weeks after EOT (third point).

The proportion of patients achieving sustained virologic response 12 (SVR12) defined as serum HCV RNA below lower level of quantification at week 12 after end of treatment) on intention to treat (ITT) basis.

Treatment-emergent adverse events (TEAEs) as reported by patients or observed by investigators during the study visits were reported and analyzed.

Statistical methods:

We presented our qualitative data as counts, proportions or percentage with the confidence interval using Wilson Score Interval Method. For quantitative data, descriptive statistics are the arithmetic mean, the standard deviation, the median and the 95% confidence interval whenever found appropriate. A repeated measures ANOVA design with one "within-factor" (ZWTAGE, ZHTAGE or ZBMIAGE) and one group with a total of 40 subjects; each subject is measured 3 times. This design achieves 89% power to test the "within-factor" if a Geisser-Greenhouse Corrected F Test is used with a 5% significance level and the actual effect standard deviation is 0.23.

RESULTS

Forty eligible patients were included in this study analysis and all received treatment with SOF/DAC. During the whole period of the study, only 1 patient was lost to follow-up after achieving the end of treatment response at the 12^{th} week visit.

The demographic and some baseline characteristics are presented in (Table, Supplemental Digital Content 1, http://links.lww.com/INF/D332).

By the end of week 4 as well as week 12 of treatment, all patients 40/40 (100%; 95% confidence interval (CI): 91.2 – 100%)) achieved viral negativity by PCR. The intent-to-treat (ITT) SVR12 rate was 39/40 (97.5%; 95% CI: 87.12 – 99.56%). The only patient who did not achieve SVR12 was lost to follow up after showing viral negativity at the end of treatment visit.

At baseline, the mean (± SD) weight was 50.75 (± 12.64) Kg and the mean ZWTAGE was 0.49 (± 0.61). After 12 weeks (at the EOT), though the mean weight did slightly increase to 51.77 Kg,

the mean ZWTAGE showed a slight reduction to 0.45 (± 0.61). At the end of the follow up period (24 weeks after baseline) the mean ZWTAGE showed a larger increase to 0.55 (± 0.55) exceeding the baseline level (Figure 1). Repeated measures analysis of variance adjusted for sex and baseline age in months did not detect the statistical significance of the differences in z scores weight for age (p = 0.56).

The mean (± SD) height as measured in centimeters (cm) at baseline was 153.25 (± 11.33) cm, with a mean ZHTAGE of – 0.32 (± 1.04). After 12 weeks (at EOT point) there was a slight increase in mean height to 154.65 (± 10.9) but the mean ZHTAGE showed a marked reduction to -0.48 (± 0.89). Whereas at the end of the follow up period (24 weeks after baseline) the mean ZHTAGE showed a slight increase to -0.36 (± 1), it did not reach the baseline level (Fig., Supplemental Digital Content 2, http://links.lww.com/INF/D333). Repeated measures analysis of variance adjusted for sex and baseline age in months did not detect the statistical significance of these differences (p = 0.301).

The unstandardized mean body mass index (BMI) as a ratio of weight in Kg over the squared height in m^2 showed a small steady numerical increase from 21.219 (± 3.22) Kg/m^2 at baseline to 21.347 (± 2.93) at week 12 and 21.593 (± 2.91) at week 24. This might reflect a relative deceleration effect on height in denominator or unbalanced weight acceleration in numerator (Fig., Supplemental Digital Content 3, http://links.lww.com/INF/D334). However this small insignificant numerical increase was not revealed as we compared the means of BMI z scores standardized for baseline age and sex (ZBMIAGE) (p = 0.9999) (Fig., Supplemental Digital Content 4, http://links.lww.com/INF/D335) (p = 0.054).

No fatalities or serious adverse events were reported during the study. Only 15 (37.5%) patients reported 23 non-serious treatment-emergent adverse events throughout the study with causality

assessment reports as possible or above. These events included nausea reported by 5 patients (12.5%), abdominal pain reported by 6 (15%), fatigue reported by 5 (12.5%), headache by 4 (10%) and pruritus or skin rash by 3 patients (7.5%). All were mild to moderate (≤ grade 2) in severity.

DISCUSSION

The intent-to-treat (ITT) SVR12 rate was 39/40 (97.5%; 95% CI: 87.12 – 99.56%). This demonstrates concordant efficacy results to other studies on DAAs treatment for chronic HCV at this age group.[9,10]

Although the repeated measures ANOVA test (Greenhouse-Geisser test of "within-subject" effect) was not statistically significant for both growth indices (ZWTAGE and ZHTAGE) but the results could suggest a relatively higher deceleration effect on height or unbalanced weight acceleration. This could also be seen from the effect on the unstandardized body mass index which showed a small steady increase throughout the study, reflecting a slight but relatively larger deceleration effect on height or unbalanced acceleration of weight.

This might partially explain the observation reported by 27 (67.5%) of the parents/care givers of the patients that they noticed a relative increase in food intake and appetite of their children shortly after starting treatment. This could at least partially compensate for the relatively more apparent (but statistically not significant) deceleration effect on linear growth during treatment.

Many other studies had addressed the issue of the effect of treatment of chronic HCV infection on growth conducted in the era of interferon based treatment.

Jonas et al., [5] had demonstrated significant deceleration effects on weight and height during interferon based therapy. Thereafter, z scores rebounded toward baseline levels but the mean

ZHTAGE remained significantly lower than baseline at the end of the 96 weeks post-treatment follow up period. [5]

While Haber et al., [6] had also reported significant decreases in height and weight z scores during treatment. Only partial recovery of ZHTAGE was observed during 5 years of follow-up in patients treated for 48 weeks.

We acknowledge the uncontrolled, non-blinded study design, the small sample size and the relatively short follow up duration as the main limitations in our study.

In summary, sofosbuvir/daclatasvir combined therapy could be a safe and effective treatment in adolescent patients 12 to 17 years of age with chronic HCV genotype 4 infections. Unlike interferon-based-therapy, we did not detect significant negative effects on linear growth or weight. Contrarily, a trend to increased appetite and insignificant weight gain were observed but further larger studies are needed to confirm.

REFERENCES:

1. AASLD-IDSA. Recommendations for testing, managing, and treating hepatitis C. http://www.hcvguidelines.org/full-report/hcv-testing-and-linkage-care. [Accessed MAY 30, 2018].
2. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu; European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2018. *J Hepatol.* 2018 Apr 9. [PAP]
3. FDA News Release. FDA approves two hepatitis C drugs for pediatric patients. FDA Web site. https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm551407.htm. Published April 7, 2017. [Accessed MAY 2, 2018].
4. Indolfi G, Hierro L, Dezsofi A, 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 Dec 28. [PAP]
5. Jonas MM, Balistreri W, Gonzalez-Peralta RP, et al. Peginterferon for Chronic Hepatitis C in Children affects Growth and Body Composition: Results from the Pediatric Study of Hepatitis C (PEDS-C) Trial. *Hepatology (Baltimore, Md)*. 2012;56(2):523-31.
6. Haber B, Alonso E, Pedreira A, et al. Long-Term Follow-Up of Children Treated With Peginterferon and Ribavirin for Hepatitis C Virus Infection. *J Pediatr Gastroenterol Nutr* 2017;64(1):89-94.
7. Comanor L, Minor J, Conjeevaram HS, et al. Impact of chronic hepatitis B and interferon-alfa therapy on growth of children. *J Vir Hepat*. 2001;8:139–47.

8. Gottrand F, Michaud L, Guimber D, et al. Influence of recombinant interferon alpha on nutritional status and growth pattern in children with chronic viral hepatitis. *European Journal of Pediatrics.* 1996;155(12):1031–4.

9. Yakoot M, El-Shabrawi MH, AbdElgawad MM, et al. Dual Sofosbuvir/Daclatasvir Therapy in Adolescent Patients With Chronic Hepatitis C Infection. *J Pediatr Gastroenterol Nutr*. 2018 Mar 22. [PAP]

10. Balistreri WF, Murray KF, Rosenthal P, et al. The safety and effectiveness of ledipasvir-sofosbuvir in adolescents 12-17 years old with hepatitis C virus genotype 1 infection. *Hepatology* 2017;66(2):371-8.

Figures/Tables legends

Supplemental Digital Content 1. Table: Demographic and some baseline characteristics

Figure 1: The mean Z scores Weight for Age (ZWTAGE) at 3 time points

Supplemental Digital Content 2. Figure 2: The mean Z scores Height for Age (ZHTAGE) at 3 time points

Supplemental Digital Content 3. Figure 3: The mean BMI at 3 time points

Supplemental Digital Content 4. Figure 4: The mean ZBMIAGE at 3 time points

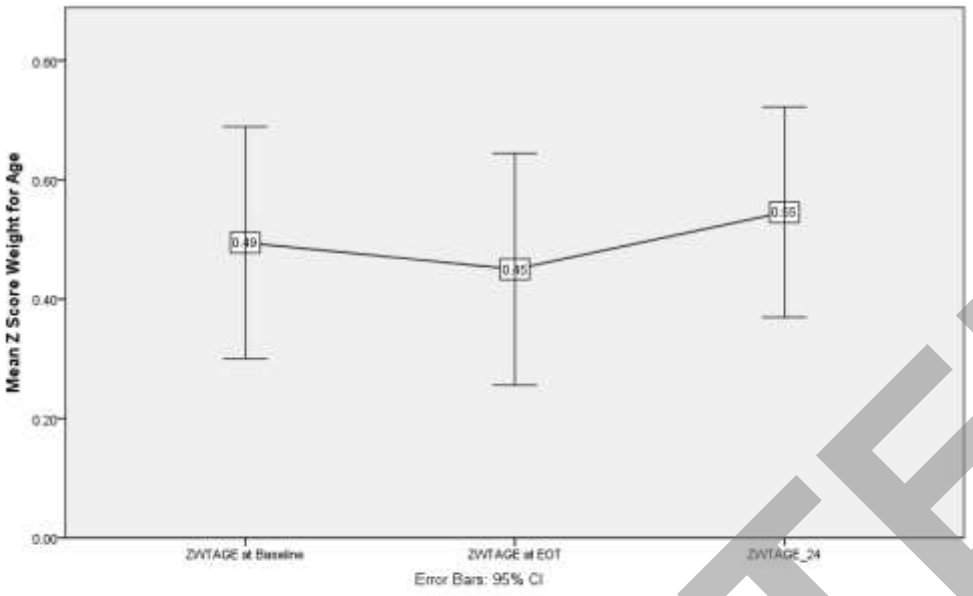

Figure 1: The mean Z scores Weight for Age (ZWTAGE) at 3 time points