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Sofosbuvir-based Therapy for Late Pregnant Women and Infant with Severe Chronic Hepatitis C: A Case Series Study

Running Title: DAAs for Mothers and Infant with CHC

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ABSTRACT

Data on sofosbuvir-based therapy for pregnant women and infant with severe chronic hepatitis C (CHC) are lacking. Two late pregnant women and one female infant with severe CHC were enrolled for treatment. Pregnant women 1 and 2 and infant 3 were 30, 33, and 1.2 years old, respectively; the gestational ages of pregnant women 1 and 2 were 31 and 26 weeks, respectively. Notably, pregnant women 1 and 2 and infant 3 had hepatitis C virus (HCV) RNA levels of 139000, 198000, and 8450000 IU/ml; alanine aminotransferase levels of 420, 781, and 220 U/L; and received sofosbuvir/ledipasvir, sofosbuvir/velpatasvir, and sofosbuvir/ledipasvir for 12 weeks, respectively. All three patients were safely cured with favorable tolerance, and two newborns were both breastfeeding and were consistently negative for the anti-HCV antibody during the one-year follow-up after birth. Additionally, two newborns and infant 3 had normal growth parameters during the follow-up year one. In conclusion, this case series study found that sofosbuvir-based therapy for pregnant women and infant with severe

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CHC is safe and effective. The data may fill the gap and provide evidence of the use of sofosbuvir-based therapy as a reference when similar severe CHC situations are encountered during clinical practice.

Keywords: Chronic hepatitis C; Effectiveness; Infant; Pregnancy; Safety; Sofosbuvir

INTRODUCTION

Hepatitis C virus (HCV) infection is one of the major causes of chronic liver diseases, leading to approximately 71 million chronically infected patients worldwide,[1] including the increasing prevalence in women at child-bearing age [1] and an estimated 3.5-5.0 million children and adolescents.[2] Although safe and well-tolerated direct-acting antiviral agents (DAAs) are available to cure HCV infection in greater than 95% of treated patients,[1-3] there is still an unmet need for treatment in some special populations with HCV infection.

For instance, DAAs were not approved for pregnant women and infants less than 3 years in the absence of safety and efficacy data; however, DAA treatment can be considered on a case-by-case basis after a thorough discussion with the patients and their families about the potential risks and benefits and in a joined-up approach with hepatology and obstetric services.[1, 2] This study reports the safety and effectiveness of two late pregnant women and one infant with severe or even life-threatening chronic hepatitis C (CHC) treated by sofosbuvir-based DAAs on a case-by-case basis.

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PATIENTS AND METHODS

Two late pregnant women (nos. 1 and 2) and one female infant (no. 3) were diagnosed with severe CHC, which was defined as alanine aminotransferase (ALT) > 5 times the upper limit of normal (ULN, 40 U/L) based on chronic hepatitis B exacerbation.[4] Additionally, no concurrent disorders, conditions, or infections other than HCV that may lead to elevated ALT levels were identified. After assessment, the multidisciplinary experts decided that antiviral treatment must be initiated. In detail, one tablet of sofosbuvir/ledipasvir (400/90 mg) and sofosbuvir/velpatasvir (400/100 mg) were administered daily to pregnant women with HCV genotypes 1b and 2a for 12 weeks, respectively. The 150/33.75 mg (slightly greater than 1/3 tablet) of sofosbuvir/ledipasvir was administered daily for this genotype 1b infant less than 17 kg for 12 weeks.[2] The drug was dissolved into milk and was fed by the infant's mother under the guidance of physicians.

The safety and effectiveness of three patients were closely monitored until at least 12 months after treatment completion. The safety evaluations included any adverse events or fluctuations in serum testing parameters during the treatment and follow-up periods. Additionally, the infants' growth parameters were also monitored as another key safety concern. The anthropometric z scores for the growth of infants were calculated based on World Health Organization (WHO) standards.[5] The effectiveness evaluations included HCV cure (defined as undetectable HCV RNA after treatment completion) and biochemical responses.

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Serum HCV RNA was monitored using a Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Test (Roche Molecular Systems, Branchburg, NJ, USA; cutoff value, 15 IU/ml). Anti-HCV reactivity was detected using a VITROS® enhanced electrochemiluminescence immunoassay (Ortho-Clinical Diagnostics, Raritan, NJ, USA). The HCV genotype was analyzed using a gene sequencing assay.

Written informed consent for the observational process was obtained from all patients prior to treatment initiation in the study. The management and monitoring strategies of this study were approved by the Ethics Committee of The First Affiliated Hospital of Zhengzhou University (2019-KY-204).

RESULTS

Baseline Characteristics

At treatment initiation, mothers 1 and 2 and infant 3 were 30, 33, and 1.2 years old, respectively, and the gestational ages of mothers 1 and 2 were 31 and 26 weeks, respectively (Figure 1 left panel). Mothers 1 and 2 had severe symptoms with ALT levels of 420 and 781 U/L, respectively. Notably, before treatment initiation, infant 3, who was infected with HCV perinatally, had a 10-month history of consistent nausea, anorexia, vomiting, detectable HCV RNA, and ALT levels of greater than 200 U/L, with the highest level of 432 U/L. Other baseline characteristics are presented in Figure 1 and Table 1.

Safety and Effectiveness

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During treatment, we found that sofosbuvir-based therapy was well tolerated, and the most common adverse event was nausea (Table 2). Two infants (nos. 1 and 2) were born with normal growth parameters and had no birth defects, and both of them received breastfeeding. Notably, mother 1 was still treated with sofosbuvir/ledipasvir during the initial 3 weeks of lactation. All three patients had undetectable HCV RNA after 2 weeks, whereas their ALT levels normalized after 12 weeks of treatment. Notably, all patients were eventually cured, which was accompanied by normalization of total bilirubin and gamma-glutamyl transferase levels (Figure 1 right panel) and no drastic changes in routine blood and renal function parameters (Figure 2).

Infants' Growth and anti-HCV Status

Infants 1 and 2 had normal growth parameters until 1.5 and 1 years of age; notably, both had consistently negative anti-HCV antibody results (Supplementary Table 1). Infant 3 had completely normal growth parameters from 3 months posttreatment to one year posttreatment (Supplementary Table 2) with consistent positivity for anti-HCV antibodies.

DISCUSSION

Currently, the safety and efficacy data of DAAs in HCV-infected pregnant women are limited, and none are licensed for use in pregnancy.[1, 2] Children aged 3-11 years can be treated with DAAs; thus, children less than 3 years of age are not eligible for treatment.[1, 2, 6] Our current study included three unique patients who

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urgently required treatment, and sofosbuvir-based DAAs were administered. Fortunately, all three patients were successfully cured with favorable tolerance and without severe adverse events or complications during treatment and until at least follow-up year one. In addition, the growth parameters were completely normal for infants 1 and 2 and were significantly improved to normal ranges after successful treatment for infant 3.

Although the "responsible inclusion of pregnant individuals in eradicating HCV" and "pregnant women with HCV prefer to be treated during pregnancy" are reasonable goals,[7, 8] safety and efficacy data are lacking. Therefore, no DAAs are licensed for use in pregnancy to date.[1-3, 6, 7, 9] Additionally, children less than 3 years old are not eligible for DAA treatment [1]. However, one acute HCV-infected infant cured by sofosbuvir/ledipasvir has been reported previously.[10]

Most recently, Jhaveri and colleagues performed a systematic review on HCV DAA treatment in pregnancy.[7] The literature search identified 1987 unique references. In total, 31 references addressed treatment for HCV in pregnancy, and only one phase 1 pharmacokinetic study of sofosbuvir/ledipasvir initiated during pregnancy in 8 individuals was identified.[11] The remaining 30 papers only discussed HCV treatment during pregnancy generally and/or called for further studies, including a pharmacokinetic study of the sofosbuvir/velpatasvir regimen

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during pregnancy that is currently recruiting with a target enrollment of only 10 participants and a target completion date of June 2023.[7]

In addition, a unique Egyptian study investigated pregnancy outcomes in women who had unintended pregnancy while on DAAs treatment.[12] A total of 100 patients were included and advised to withhold DAA therapy and continue follow-up in viral hepatitis and obstetrics centers until delivery. All patients received a 12-week regimen of DAA treatment; 95, 3, and 2 patients were treated with sofosbuvir plus daclatasvir, sofosbuvir/daclatasvir plus ribavirin, and paritaprevir/ritonavir/ombitasvir plus ribavirin, respectively. Eventually, 9 patients completed the full DAA course, and 91 stopped between on-treatment weeks 4 and 8. Of the 9 patients who completed the full course of DAAs, 7 (77.8%) women delivered normal full-term newborns, whereas the other 2 women were lost to follow-up. At the posttreatment week 12 visit, all 7 women achieved sustained virological response, i.e., HCV cure; additionally, no major antiviral-related adverse events were reported. Notably, there are some differences between this Egyptian study and our study. First, the DAA regimens used in the two studies were different. Second, pregnancy occurred unintentionally during DAA treatment in the Egyptian study, and DAAs were actively used to treat severe CHC during late pregnancy in our study. Third, two normal newborns were breastfed, tested for anti-HCV antibody, and followed up until at least one year in our study, these data are lacking in the Egyptian study. Regardless of these

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differences, the two studies initially indicated that DAAs may be safe for fetal outcomes and effective during pregnancy.

In the clinic, CHC progresses slowly, and significant ALT elevation is infrequently noted. We hypothesized that the significant ALT elevations of the two mothers were related to pregnancy in the current study. Of note, both mothers had increased total bilirubin levels, and mother 1 had a significant elevation greater than 5 times the ULN. Additionally, two mothers had gradually severe accompanying symptoms during pregnancy. Considering the life-threatening risk of two mothers and their fetuses as well as 10 months of consistent nausea and other symptoms for infant 3, we decided to treat them immediately, and sofosbuvir-based DAAs were administered. Notably, all three patients were safely cured, and all three infants' growth conditions were normal compared with the WHO standards.

Pregnant women with CHC have increased rates of adverse outcomes during pregnancy, and mother-to-child transmission occurs in 5% (3), including infant 3 in this study. Infant 3 was one year and two months plus 3 days of age at the time of sofosbuvir/ledipasvir treatment initiation. This infant's mother, who was born in 1989, had a blood transfusion history in 1992 and was diagnosed with HCV infection at 3 months of pregnancy with an HCV RNA level of 6620000 IU/ml and HCV genotype 1b and normal liver function. However, the hepatologist refused to treat her HCV infection during pregnancy according the HCV

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guidelines.[1, 2] In addition, she also did not want to receive treatment during pregnancy because the hepatologist told her that the HCV guidelines do not recommend treatment and the mother-to-child transmission (MTCT) possibility is low. Of note, infant 3 did not receive breast milk from her mother. Additionally, our previous study performed liver biopsies in 163 children aged 1-5 years (median 2.6 years) with iatrogenic CHC and found that a total of 23.9% (39/163) of cases exhibited grade 2 inflammatory activity, 30.1% (49/163) exhibited stage 2/3 liver fibrosis, and only 0.6% (1/163) and 9.8% (16/163) exhibited complete grade 0 inflammatory activity and stage 0 liver fibrosis, respectively, although these children newly acquired CHC.[13] Given the abovementioned risks and hazards concerning HCV MTCT and liver injury in CHC infants, the treatment of pregnant women and children under 3 years old represent the next two puzzle pieces in the field of hepatitis C treatment. To the best of our knowledge, this study is the first report concerning DAA treatment in pregnant women and infants with severe CHC worldwide.

The currently approved DAAs seem to cross the placenta and transfer into breast milk, but no safety hazard from animal studies have been reported.[9] Our study supports these findings based on findings from two mothers treated with sofosbuvir/ledipasvir and sofosbuvir/velpatasvir for 9 and 12 weeks, separately, during late pregnancy and their 2 babies receiving breastfeeding. Of note, infant 1

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received an initial 3 weeks of breastmilk while his mother was receiving simultaneously sofosbuvir/ledipasvir treatment.

Conclusively, this case series study found that sofosbuvir-based therapy for pregnant women and infant with severe CHC is safe and effective. Although our study has the limitation of a small sample size, this study supports the use of sofosbuvir-based therapy in similar severe or life-threatening clinical situations. Future large-scale validation studies are warranted.

Authors' contributions. QLZ and ZJY contributed equally to this work. QLZ, ZJY, and FPJ contributed to the study concept, design, and critical review of the manuscript. QLZ, JL, HXZ, BW, XPD, ZMC, and GLC contributed to the patient care, data collection, interpretation, and analysis. QLZ and ZJY contributed to the drafting the manuscript. All authors read and approved the final manuscript.

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Data availability statement. All data relevant to the study are included in the article.

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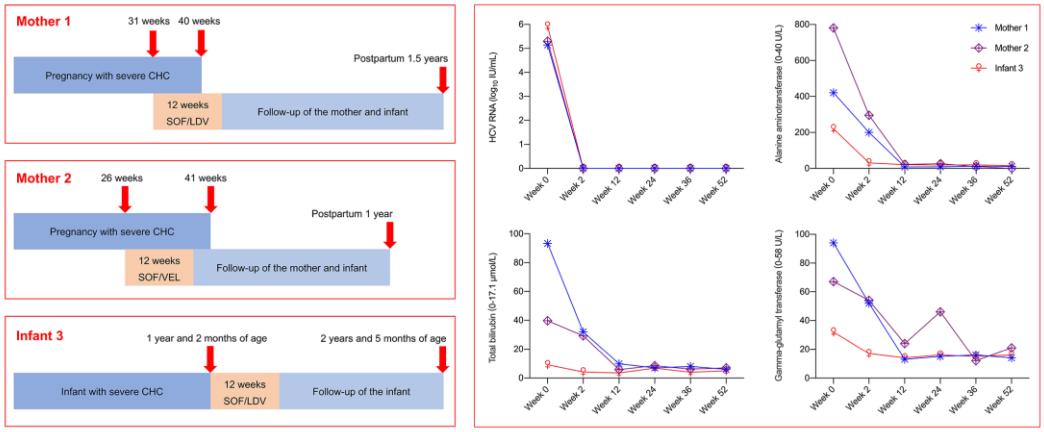

Figure 1. Management strategy (left panel) and effectiveness (right panel) of two mothers and one infant with severe CHC. Abbreviations: CHC, chronic hepatitis C; HCV, hepatitis C virus; SOF/LDV, sofosbuvir/ledipasvir; SOF/VEL, sofosbuvir/velpatasvir.

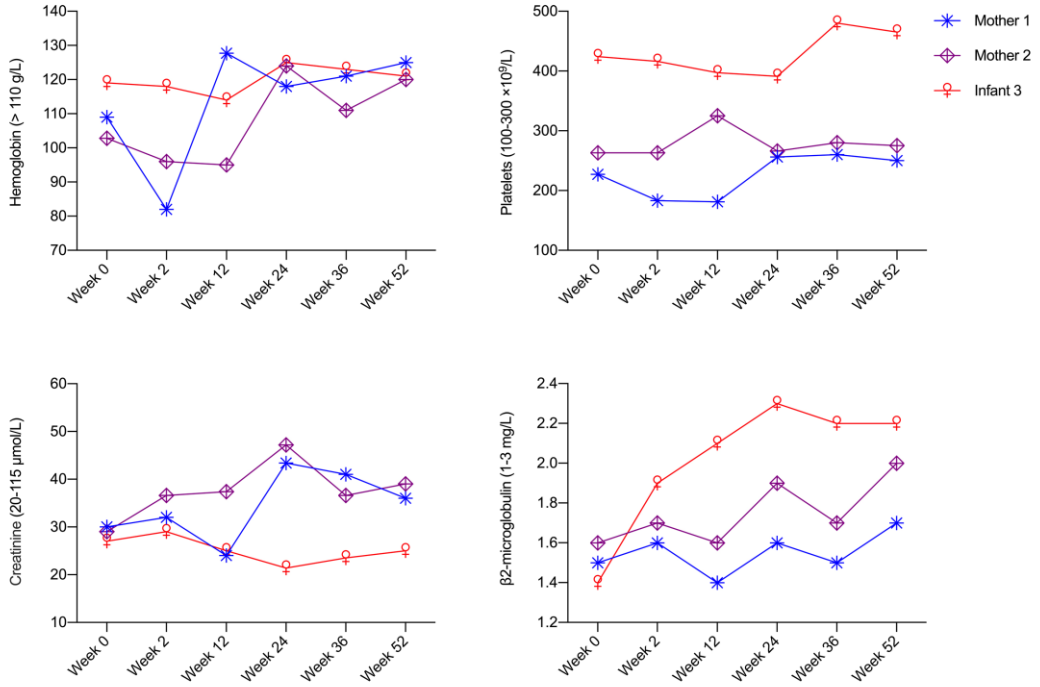

Figure 2. Dynamic changes in serum hemoglobin, platelets, creatinine, and β2-microglobulin levels during and after the completion of treatment.

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Table 1. Characteristics of two mothers and one infant with severe chronic hepatitis C at treatment initiation

Characteristics (before treatment)	**Mother 1**	**Mother 2**	**Infant 3**
Female	Yes	Yes	Yes
Age, year	30	33	1.2
Primipara	Yes	Yes	-
Suspected transmission route of HCV	Unknown	Transfusion	MTCT
HCV RNA detectable before treatment	5 years	6 years	10 months
Gestational age, weeks	31	26	-
Nausea	Yes	Yes	Yes
Vomiting	Yes	Yes	Yes
Anorexia	Yes	Yes	Yes
Fatigue	Yes	Yes	Yes[§]
Dizziness	Yes	Yes	-[§]
Insomnia	Yes	Yes	Yes[§]
Headache	No	Yes	-[§]
HCV RNA, IU/ml	139000	198000	8450000
HCV genotype	1b	2a	1b
Alanine aminotransferase (0-40 U/L)	420	781	220
Aspartate aminotransferase (0-40 U/L)	351	535	120
Alkaline phosphatase (35-105 U/L)	172	109	291

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Gamma-glutamyl transpeptidase (0-58 U/L)	94	67	32
Total bilirubin (0-17.1 μmol/L)	93.3	39.7	9.2
Hemoglobin (≥ 110 g/L)[†]	109	102.8	119
Platelets (100-300 × 10^9/L)	227	263	424
Creatinine (20-115 μmol/L)	30	29	27
β2-Microglobulin (1-3 mg/L)	1.5	1.6	1.4
eGFR, ml/min/1.73 m^2	148	146.6	-
Systemic disorders[‡]	No	No	No
Other liver diseases[‡]	No	No	No
Other infections[‡]	No	No	No
Treatment regimen	SOF/LDV	SOF/VEL	SOF/LDV
Treatment duration	12 weeks	12 weeks	12 weeks

[†]Hemoglobin of less than 110 g/L indicates anemia during pregnancy, and ≥ 110 g/L indicates normal for boys and girls aged 0.5-4 years old. [‡]The excluded disorders, conditions, or infections included hypertension, diabetes, hyperlipidemia, chronic obstructive pulmonary disease, coronary artery disease, chronic kidney disease, malignancy, arrhythmia, asthma, smoking, alcoholism, cirrhosis, inherited metabolic liver disease, autoimmune liver diseases, drug-induced liver injury, nonalcoholic fatty liver disease, upper respiratory tract infection, chlamydia pneumoniae, hepatitis (A, B, D, and E), human immunodeficiency virus, cytomegalovirus, and Epstein–Barr virus. [§]Infant 3 could not express these symptoms, but her mother described that she did not like moving and playing at all and had multiple awakenings during sleeping. Abbreviations: HCV, hepatitis C virus; eGFR, estimated glomerular filtration rate; MTCT, mother-to-child transmission; SOF/LDV, sofosbuvir/ledipasvir; SOF/VEL, sofosbuvir/velpatasvir.

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Table 2. Adverse events of the two mothers and one infant during treatment

Adverse events[†]	**Mother 1**	**Mother 2**	**Infant 3**
Nausea	Yes	Yes	Yes
Vomiting	Yes	Yes	Yes
Anorexia	Yes	Yes	Yes
Fatigue	Yes	Yes	Yes[‡]
Dizziness	Yes	Yes	-[‡]
Insomnia	Yes	Yes	Yes[‡]
Headache	No	Yes	-[‡]

[†]The adverse events that occurred during treatment also existed before treatment; notably, these symptoms disappeared gradually with treatment. [‡]Infant 3 could not express her feelings, but her mother described that she still did not like moving and playing and had multiple awakenings during sleeping, especially during the first month of treatment; notably, her symptoms gradually disappeared from the third month of treatment.

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