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ORIGINAL ARTICLE

Safety and efficacy of treatment for chronic hepatitis C during pregnancy: A prospective observational study in Srinagar, India

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Abstract

In India, the estimated prevalence of antenatal HCV infection is 0.3%–2.8%, and the rate of mother-to-child transmission has been estimated at 5%–15%. HCV treatment during pregnancy could reduce maternal complications from HCV infection, prevent transmission to the infant, and reduce HCV infection overall in women of childbearing age. However, there are limited studies of HCV treatment with direct-acting antiviral medications during pregnancy, and therefore, direct-acting antivirals are not commonly used for treatment during pregnancy. We describe our institutional experience in this prospective observational study over 3 years at the Sher-I-Kashmir Institute of Medical Sciences, Srinagar, India. Patients with chronic hepatitis C in pregnancy were enrolled and treated with ledipasvir and sofosbuvir after the first trimester. Primary end points were sustained virologic response at 12 weeks, adverse drug reactions, and congenital malformation of the infant. The secondary end point was the transmission of HCV infection to the infant. We enrolled 26 patients in our study. The mean age was 28 years (range of 21–36 y). All patients were noncirrhotic and treatment-naive. The mean HCV RNA before treatment was 9.2 ×10^5 IU/ml. Among the enrolled patients, 19 (73%) were genotype 3, 5 (19%) were genotype 1, and 2 (8%) were genotype 4. All patients achieved sustained virologic response at 12 weeks. Some patients reported nausea (27%), headache (27%), and fatigue (16%). All patients had institutional delivery, and no infant was found to have congenital malformations. No child had detectable HCV RNA at 6 months of age. To our knowledge, we here report results from the largest cohort of pregnant women treated for HCV infection globally. Ledipasvir and sofosbuvir were well tolerated and highly effective for both HCV cure in the mother and elimination of mother-to-child transmission. No congenital

Abbreviation: MTCT, mother to child transmission.

abnormalities were detected in our cohort. Elimination of mother-to-child transmission is urgently needed, and this study has shown that treatment of HCV during pregnancy may be a pragmatic approach for the greater benefit of both mother and the newborn.

BACKGROUND

HCV infection represents a significant health problem in women of childbearing age during pregnancy. About 1%–8% of pregnant women have positive markers of HCV infection, and the prevalence is lower in Western/Northern countries compared with Eastern/Southern countries.[1,2] In India, the estimated prevalence of antenatal HCV infection is 0.3%–2.8%;[3,4] In the United States, due to the increased use of opioids in women of childbearing age, HCV infection at delivery has increased by 89% from 2009 to 2014, and the prevalence of maternal HCV infection has increased by 163% in the same period with wide geographic variations.[5,6] Accordingly, in the United States and several other countries with substantial opioid use, it is now recommended to test all pregnant women for HCV.[7] The primary mode of HCV transmission is exposure to infected blood from injection drug use, blood transfusion, surgical procedures, or sexual transmission. Other modes of transmission include mother-to-child transmission (MTCT), sharing of contaminated devices, occupational exposure, and local traditional practices (needle tattooing and leech therapy). Most studies from India could not find the main mode of transmission of HCV in women, with most partners found to be negative on testing.[8]

HCV infection has been found to be associated with adverse pregnancy outcomes.[9–13] HCV infection has been associated with intrahepatic cholestasis of pregnancy. The odds of developing intrahepatic cholestasis of pregnancy are 20-fold higher in HCV-infected pregnant women than in the general population.[14]

Following the introduction of universal HCV screening for blood donations, MTCT of HCV has become the leading cause of pediatric HCV infection.[15–17] MTCT occurs at an overall rate of 5%–15%.[18,19] Present-day evidence has shown the correlation between maternal viral HCV titer and the risk of neonatal infection.[20] Higher maternal HCV viral titer, prolonged membrane rupture during labor ($\geq$6 h), and use of internal fetal monitoring during labor are risk factors for the vertical transmission of HCV.[21]

At present, no drug for the treatment of chronic hepatitis C is recommended by any guidelines during pregnancy because of a lack of human studies. On the basis of limited animal data, sofosbuvir, ombitasvir, paritaprevir, ritonavir, and ledipasvir have not been demonstrated to confer a risk to the fetus.[19,22] However, no direct-acting antiviral therapy has yet been approved to treat HCV infection in pregnancy due to the lack of human studies. Recently, the pharmacokinetics of ledipasvir/sofosbuvir in 9 pregnant patients in the United States demonstrated high safety and efficacy when started during the second or third trimester.[23]

Keeping in view these findings, along with the high efficacy of this combination in HCV genotype 3 (prevalent in the Indian subcontinent),[24,25] we describe our experience in this prospective observational study of the use of ledipasvir and sofosbuvir for HCV infection during pregnancy to assess treatment efficacy, fetomaternal complications, and the possibility of decreasing MTCT.

METHODS

Study design and oversight

This was a single-center experience of an observational, prospective study conducted over a period of 3 years from March 2016 to February 2019 at the Sher-I-Kashmir Institute of Medical Sciences, Srinagar, India. The study was conducted after obtaining ethical clearance from the Sher-I-Kashmir Institute of Medical Sciences Institutional Ethics Committee. This is the only institution providing specialized hepatology services in the state of Jammu and Kashmir. Two maternity hospitals are attached to the institution, which provide universal free screening for HCV and antenatal care to pregnant women.

All pregnant patients who tested positive for anti-HCV at these 2 maternity hospitals were referred for specialist consultation and consideration for treatment. Only those patients who were willing to be treated during pregnancy and gave written consent were enrolled. In the consent form, the risks and benefits of the medications were clearly defined. The maternal risks defined were medication-related side effects, including nausea, headache, and fatigue. The benefits defined were the potential for curing HCV in the mother, prevention of MTCT, and improving obstetric outcomes at delivery. Before starting treatment, HCV RNA and genotype testing were done in all patients. Plasma HCV RNA levels were measured with the use of a real-time reverse transcriptase PCR assay (COBAS TaqMan HCV Test, version 2.0, Roche), and the lower limits of

both detection and quantification were 15 IU per ml. The genotype of HCV was determined by kit-based assays (Abbott RealTime HCV Genotype II Kit). Besides, investigations included hemogram, renal parameters, liver function tests, HBsAg, HBcAb, HIV antibody, ultrasonography for the detection of HCC, and transient elastography by Fibroscan. Inclusion criteria were the age of 18–39 years, willingness to provide written consent, singleton pregnancy, no known fetal malformations, negative HBsAg, and negative HIV antibody, which were included in the study. Exclusion criteria were cirrhosis by transient elastography on Fibroscan and previous HCV treatment. Patients with HIV coinfection were excluded to ensure a uniform and homogeneous group of participants in the study. Participants were treated with coformulated tablets of sofosbuvir and ledipasvir (400 + 90 mg) once a day for 12 weeks based on our institutional HCV treatment protocol for patients who were noncirrhotic and the standard availability of these treatment options at that time. Participants were treated during the second or third trimester of pregnancy, with ideal treatment initiation at 15–20 weeks. Medicines were provided free of cost to all patients, which was a state government policy.

Laboratory assessments and efficacy end points

The primary efficacy end point of the study was sustained virologic response at 12 weeks following completion of treatment, and the secondary end point was MTCT at 6 months postpartum. Blood samples for HCV RNA were obtained at week 4 for rapid viral response, week 12 for end of treatment response, and week 12 from the end of completion of treatment for the assessment of sustained viral response. Patients were sent visit reminders by phone call and short message service. If a participant was absolutely unable to attend the visit, blood sampling was done at her home. Children were tested for IgG anti-HCV at 6 months of age by ELISA, and those found positive were tested for HCV RNA. Sustained viral response 12 was defined as an HCV RNA level of less than 15 IU per ml 12 weeks after the end of treatment. Virologic failure was defined as an increase in the HCV RNA level of 100 IU per ml or more after a measurement showing an HCV RNA level of less than 15 IU per ml during treatment or an increase in the HCV RNA level of more than 1 log10 IU per ml from the nadir during the treatment period. Virologic relapse was defined as HCV RNA level of less than 15 IU per ml at the end of treatment, followed by HCV RNA level of at least $\geq$15 IU per ml between the end of treatment and 12 weeks after the last dose of the drug.

Safety assessments

Safety assessments included the evaluation of adverse events by a structured questionnaire, vital signs, physical examination, electrocardiography, and laboratory testing at baseline, 4, 12, and 12 weeks after treatment. Baseline ultrasonography was done for fetal well-being and repeated at the end of treatment by a radiologist for any abnormality. The neonatal examination was done by a pediatrician to report any congenital malformation (defined as structural abnormalities with surgical, medical, or cosmetic significance).

Statistical analysis

A descriptive analysis of the primary end points was conducted after all the enrolled patients had completed the posttreatment week 12 visit. We determined the percentage of patients who met the criteria for each of the primary and secondary end points of the study.

RESULTS

Characteristics and pregnancy outcomes

The baseline demographic and disease characteristics of enrolled patients are shown in Table 1. Out of 39 patients approached for enrolment in the study, 26 patients were enrolled. Twelve patients did not consent due to safety concerns. All patients were of Asian ethnicity. The patients ranged from 21 to 36 years of age (median:

TABLE 1 Baseline demographic and clinical characteristics of participants (n = 26).

Baseline characteristic	Mean ± SD
Age	28 ± 3.5 y
Bilirubin	0.9 ± 0.3 mg/dl
Alanine transaminase	69 ± 37 IU/L
Albumin	3.6 ± 0.4 gm/dl
Creatinine	0.6 ± 0.25 mg/dl
International Normalized Ratio (INR)	1.07 ± 0.09
HCV RNA	9.2×10^5 copies/L
Baseline fibrosis by kPa (Fibroscan)	5.2 ± 1.6 kPa
Platelets	$187 \pm 68 \times 10^3$/μL
Trimester of treatment, n (%)	
Second	15 (58)
Third	11 (42)
Genotype, n (%)	
1	5 (19)
3	19 (73)
4	2 (8)

Abbreviation: INR, International Normalized Ratio.

28 y). HCV risk factors included ear piercing (20/26), nasal piercing (10/26), and dental extraction (4/26) patients. No patient had a history of i.v. opioid use. Mean liver stiffness as measured by Fibroscan was 5.2 kpa. A majority of the patients were genotype 3 (19 of 26; 73%). Five of 26 (19%) were genotype 1, and 2 of 26 (8%) were genotype 4. The mean HCV RNA was $9.2 \times 10^5 \pm 3.6 \times 10^5$ copies/ml. 15/26 (58%) initiated treatment during the second trimester, and 11/26 (42%) initiated treatment during the third trimester. All patients had in-hospital full-term deliveries with a mean gestational age of 280.7 ± 12 days. In all, 22/26 (85%) had normal vaginal deliveries, while 4/26 (15%) had delivery by caesarian section. None of the patients developed intrahepatic cholestasis of pregnancy.

Efficacy

Treatment with sofosbuvir and ledipasvir for 12 weeks resulted in rapid virologic response (26/26; 100%) and sustained virological response (26/26; 100%) in all participants (Table 2). Among 26 children born to the treated mothers, only 4 of 26 (15%) children were found to be anti-HCV positive at 6 months of age; however, none (0/4) had detectable HCV RNA (Table 3).

Safety

None of the study participants had to discontinue the therapy due to any adverse drug reactions. The most frequently reported side effects were nausea (7/26; 27%), headache (7/26; 27%), and fatigue (4/26; 15%). No adverse effects were reported by 8 of 26 (31%) participants (Table 4). No major or minor maternal or fetal adverse events were recorded. There were no intrauterine, peripartum, or neonatal deaths. No neonate needed intensive care or assisted ventilation. All neonates were reported to have no congenital malformations on clinical examination and detailed pediatric evaluation.

DISCUSSION

To our knowledge, we present here the outcomes of the largest group of individuals treated for HCV infection during pregnancy reported to date. Among the 26 treated with 12 weeks of ledipasvir and sofosbuvir in pregnancy in this study, all achieved sustained viral response 12, and there was no recorded HCV vertical transmission to the infants. There were no detected congenital malformations or major adverse events resulting in treatment discontinuation. Minor adverse drug reactions were similar to those previously reported for this regimen.

Our findings regarding the safety and effectiveness of HCV treatment in pregnancy are comparable to previously published studies with smaller sample sizes. A previous phase 1 pharmacokinetic study of antenatal HCV treatment by Chappell et al with ledipasvir and sofosbuvir reported a 100% cure rate in all 9 enrolled pregnant patients with no safety issues with regards to maternal health, pregnancy outcomes, and infant health.[26] Kushner et al have also shown similar results in a study of 7 patients with HCV infection treated by direct-acting antivirals during pregnancy.[27] Tomar and Martinez have reported 3 pregnant females with HCV infection treated during the third trimester of pregnancy without any safety issues on maternal and fetal outcomes.[28] Accidental exposure to direct-acting antivirals in the first trimester of pregnancy in 7 women was reported by El-Sayed et al; all 7 patients had normal full-term deliveries without any congenital anomalies in any infant.[29]

In our study, we observed no loss-to-follow-up by the participants. This high rate of treatment adherence may have been facilitated by the provision of free medical services (including free consultations, medicines, and laboratory tests), a highly motivated study team, and frequent outreach by phone calls and short message service.

This study has several limitations. There was a possibility that congenital abnormalities could go undetected by pediatric examinations. The evaluations of the infants conducted in this study were designed to reflect pediatric assessments that can be practically conducted by clinicians in our setting. This sample size was not big enough to make a definitive statement on the safety and efficacy of this medication at the

TABLE 2 Virologic response of study participants (n = 26).

End point	N (%)
4 wks of treatment, n/total n (%) Rapid virologic response (RVR)	26/26 (100)
12 wks of treatment, n/total n (%) End of treatment response (ETR)	26/26 (100)
12 wks Posttreatment, n/total n (%) Sustained virologic response (SVR12)	26/26 (100)

TABLE 3 HCV RNA status in infants (n = 26).

End point	n (%)
Positive HCV RNA Status (Infants) 4 wks, n/total n (%)	4/26 (15)
Positive HCV RNA Status (Infants) 12 wks, n/total n (%)	0/4 (0)

TABLE 4 Adverse drug reactions.

Adverse drug effect	Frequency	%
Fatigue	4/26	16
Headache	7/26	27
Nausea	7/26	27
None	8/26	31

population level. As a single-arm trial, there was no control group for comparison, and this study design is not adequate enough to definitely establish the safety and efficacy of the intervention. Given that there were no women with intravenous drug use we would state that these findings may not be generalizable to contexts where the HCV epidemic in women of reproductive age is largely due to intravenous drug use. Such populations may have different and more difficult psychosocial circumstances. Specific measures were taken to ensure high treatment adherence, but those measures may not be possible in other settings.

CONCLUSIONS

Pregnancy is a period when women highly utilize services to improve their health and that of their unborn offspring. Since pregnant women are frequently in touch with the health care system for antenatal visits, this provides an excellent opportunity to integrate various screening and treatment protocols. The benefits of treatment of HCV are immense, including prevention of cirrhosis, HCC, liver transplantation, and improvements in physical, mental, and social well-being. All efforts should be directed to treat women of childbearing age with chronic HCV before conception, with preconception counseling regarding delaying pregnancy until HCV treatment is completed. However, with the increased rate of detection of HCV during pregnancy, it has become imperative to manage HCV during pregnancy. Our study showed that the treatment with the combination of sofosbuvir and ledipasvir is well tolerated, effective, and safe during pregnancy in our context and, as such, should be considered during pregnancy to prevent the vertical transmission and fetomaternal comorbidity associated with HCV infection. Moving forward, HCV treatment exposure registries, such as the TiP-HepC registry and clinical trials for HCV treatment in pregnancy, are needed.

CONFLICTS OF INTEREST

The authors have no conflicts to report.

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