Case report

Successful sofosbuvir lead-in monotherapy for the treatment of hepatitis C virus (HCV) infection in a pregnant woman living with HIV

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SUMMARY

A 30-year-old woman living with HIV was diagnosed with genotype 2b hepatitis C virus (HCV) infection during the second trimester of her pregnancy. She had achieved virologic suppression on an HIV protease inhibitor-based regimen and had recurrent genital herpes simplex virus infection managed with antivirals. Given the risk of perinatal transmission of HCV and to avoid performing a caesarean section, after multidisciplinary consultations and consideration of the limited data on safety on HCV direct-acting antivirals (DAAs) in pregnancy, she consented to and was successfully treated with a 6-week lead-in course of sofosbuvir (SOF) alone followed by a 6-week course of SOF and velpatasvir postpartum. This resulted in cure of her HCV infection. The neonate tested negative for HCV at birth and was healthy without birth defects 2 years postdelivery. Our case highlights a successful HCV treatment approach in a pregnant woman with newer DAAs.

BACKGROUND

Hepatitis C virus (HCV) infection is common among people living with HIV (PLWH), the majority of whom acquire the disease by engaging in unsafe injection practices. In the USA, it has been observed that the prevalence of HCV infection among pregnant women at time of delivery almost doubled over a 5-year period (2009–2014).[1] For these women, HCV infection may be associated with adverse perinatal outcomes including preterm delivery and low birth weight.[2] In recent years, there have been an expanding number of very effective direct-acting antiviral (DAA) therapies for HCV with a typical regimen comprised of two drugs from two different antiviral classes. These have good tolerability and excellent disease cure rates even among PLWH (a previous predictor of poorer response in the pre-DAA treatment era)

For pregnant women living with HIV and HCV, perinatal transmission of HCV may occur in up to 17% of cases. Perinatal prevention strategies to date include caesarean section although there are limited data on its efficacy. Older treatment regimens for HCV that included ribavirin are contraindicated for use in pregnancy. In addition, there are limited data on the safety of novel HCV DAAs in pregnancy and during breastfeeding. Novel HCV therapies have not been studied for use in children.

The first generation non-structural protein 5B (NS5b) RNA-dependent RNA polymerase inhibitor, sofosbuvir (SOF), has been shown to be safe in animal studies and is therefore considered safe for use in pregnancy where the benefits of use outweigh risks. This informed a phase I study conducted by Chappell and colleagues[3] that showed similar efficacy and safety of SOF in combination with ledipasvir for the treatment of HCV genotypes 1, 4, 5 and 6 in pregnant women compared with non-pregnant individuals. This case report describes the successful use of lead-in SOF monotherapy followed by combination treatment with SOF and velpatasvir for genotype 2 HCV infection in a pregnant woman living with HIV.

CASE PRESENTATION

A woman in her 30s who was a G4P0030 at 15 weeks of gestation was referred to us by her high-risk obstetrics group for expert opinion on the management of HCV infection in pregnancy. She had a previous medical history of well-controlled HIV infection on combination antiretroviral therapy—atazanavir boosted with ritonavir along with emtricitabine and tenofovir disoproxil fumarate (ATV/r+FTC/TDF), and opioid use disorder (heroin) for which she was on sublingual buprenorphine maintenance therapy. She also had a history of recurrent genital herpes simplex virus (HSV) infection for which she was on suppressive valacyclovir. She had discontinued oral contraceptive pills 5 months previously desiring a pregnancy. She subsequently presented after multiple missed menstrual periods and was found to have a positive office urine pregnancy test.

INVESTIGATIONS

Her absolute CD4 count was 939 cells/µL and her HIV-1 RNA level was not detected. White blood count was 5600/µL with a normal differential, haemoglobin was 128 g/L and platelet count was 169 000 cells/µL. Her hepatitis C antibody was positive, viral RNA was quantified as 19 200 000 IU/mL (7.28 logs) and genotyped as 2b. Liver function tests were normal except for an elevated indirect bilirubin that was attributable to atazanavir use. AST to Platelet Ratio Index (APRI) score was 0.59 and Fibrosis-4 (FIB-4) score was 1.02 consistent with not having advanced fibrosis/cirrhosis. She

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showed immunity to hepatitis A and B viruses as detected by antibody assays.

Management dilemma

The rate of vertical transmission (VT) of HCV in viremic women is approximately 6%.[4] However, in HIV coinfected women, the rates of transmission are significantly higher and can be up to 10%–17%.[4 5] This is thought to be secondary to the host's immunosuppressed state and associated higher level of HCV viremia. It remains unclear whether this occurs in utero or during delivery. A history of injection drug use is also an independent risk factor for VT.[6] While there are several HCV DAAs, limited data exists on their safety and efficacy during pregnancy. Furthermore, current guidelines favour deferring treatment until the patient is postpartum.[7] Given the potential for VT, the increased risk with high viral loads and HIV coinfection, we were faced with a dilemma—treat now or treat later? This was particularly salient given that DAAs are not approved for treatment in children under 12 years of age and thus treatment is typically deferred until then given the observed slow progression of liver disease in children and significant rates of spontaneous clearance when infected.[8]

TREATMENT

After a multidisciplinary discussion among her consultants which included hepatologists, HIV and maternal–foetal medicine specialists, as well as a robust discussion with the patient on the risks and benefits of treatment versus non-treatment, SOF monotherapy was started at week 34 of pregnancy. An investigational new drug (IND) application was not filed as we anticipated a short lead in period with SOF prior to initiation of combination therapy. SOF alone was selected as it had the longest term data on safety in pregnancy of any of the approved DAAs and because data on companion drugs were limited at the time. The expectation was to achieve a significant reduction in her viral load at the completion of 4 weeks of therapy sufficient to prevent perinatal transmission, and with a plan to induce labour at 38 weeks and to transition afterwards to SOF/velpatasvir (VEL) to complete a 12-week course of therapy. Impressively, after just 2 weeks of single agent therapy, her HCV viral load declined to 156 IU/mL (2.19 logs). Given this decline, there was no indication for induction of labour and the management plan was to allow her to enter labour spontaneously with vaginal delivery to be attempted.

OUTCOME AND FOLLOW-UP

She ultimately underwent caesarean delivery as she had active genital HSV infection at 40+1 weeks (in the setting of poor adherence to valacyclovir), with resultant delivery of a healthy baby girl. At the time of delivery, unfortunately, the maternal HCV viral load was not repeated. At birth, however, the baby's HIV RNA viral load was negative and HCV viral load testing was negative. She elected not to breastfeed her baby, consistent with current guidelines for the prevention of perinatal transmission of HIV. Ultimately, she completed 6 weeks of SOF and 6 weeks of SOF/VEL (a total of 12 week of HCV antiviral therapy). At completion of HCV therapy, the viral load was undetectable. She achieved a sustained virologic response (SVR), that is, an undetectable viral load 12 weeks after completion of HCV DAA therapy consistent with cure. The baby remains in care of paediatricians and remains healthy with no evidence of teratogenicity 2 years after birth with plans for indefinite follow-up.

DISCUSSION

Our case illustrates an adaptive approach to managing HCV infection in a pregnant PLWH in order to prevent VT in a high-risk situation. The data on DAAs are unknown or very limited in pregnancy and breastfeeding, however given the increased risk of VT in HIV-HCV coinfected cases, we favoured treatment to prevent transmission to the baby. However, even though the desired outcome was achieved with the newborn (ie, being HCV-uninfected at birth), it remains unclear if it was attributable to the treatment received or not, and as such, more data are needed to determine if this approach is effective or not.

Multiple antivirals have activity against genotype 2 HCV infection and treatment typically involves two drugs used in combination. Of these, SOF has certain characteristics that made it a favourable treatment option for this patient. SOF is a chain-terminating nucleotide analogue inhibitor of the NS5B HCV RNA-dependent RNA polymerase and has pan-genotypic activity. SOF has a high barrier to resistance, which is usually conferred by acquisition of the rare S282T mutation.[9 10] SOF has a favourable tolerability profile and did not have any significant interactions with her antiretroviral treatment regimen. More importantly, in animal studies there were no adverse effects or teratogenicity observed during pregnancy[11] and at the time of interaction with the patient, there was reasonable clinical experience with the drug with no reported adverse pregnancy or fetal outcomes reported. We elected not to use any companion drugs with SOF including velpatasvir or daclatasvir at the time as there were even more limited data with their use in pregnancy and not much added benefit was expected in the context of our plan to treat her for a limited time predelivery and subsequently introduce a full regimen postpartum. Moreover, daclatasvir and velpatasvir also interact with the TDF component of her antiretroviral regimen, which would have resulted in higher TDF levels if coadministered although this could have been mitigated by a switch of her antiretroviral regimen.

To our knowledge, only case reports exist of HCV treatment with SOF monotherapy for the entire course of treatment. One such case report involved an immunosuppressed patient who did not achieve SVR.[12] In our case, we elected to introduce dual therapy immediately after delivery in order to mitigate the risk of treatment failure or relapse. Given the rapid virologic decay only 2 weeks into therapy, we considered it reasonable to complete, rather than re-initiate, a 12-week course with SOF/VEL combination regimen postpartum.

There are limited data regarding which modes of delivery and peripartum procedures increase or decrease the risk of perinatal HCV transmission. Experts suggest that invasive procedures during the peripartum period such as fetal scalp monitoring and forceps delivery are best avoided.[7] Studies have also shown that transmission occurs at substantially higher rates when HCV viral loads are above 10^7 IU/mL but the data on vaginal delivery versus caesarean section for preventing or decreasing HCV transmission to infants by viremic mothers are inconclusive. Also of note is that HCV can also be found in human milk and colostrum, but per the CDC, breastfeeding is not considered a risk for VT of HCV unless there is the presence of cracked or bleeding nipples,[13] however for HIV coinfected mothers, it is discouraged due to risk of transmission of the latter infection. Postexposure prophylaxis after birth or during breastfeeding for prevention of transmission of HCV to infants is not recommended. The presence of components of SOF and velpatasvir or their metabolites in breast milk has not been studied such that the risks to babies are unknown.[14] Our patient elected not to breastfeed her baby in accordance with guidelines

for preventing VT of HIV. On the other hand, in the event that a transmission event occurs, the use of HCV DAAs has not been studied in young children (<12 years of age).

In summary, while this case highlights a successful approach to HCV treatment in pregnancy, it also exposes many knowledge gaps in the management of this unique patient population.

Learning points

- HIV-hepatitis C virus (HCV) coinfected women are more likely to transmit HCV to their newborn than HCV monoinfected women.
- Sofosbuvir monotherapy lead-in treatment may be an option to prevent HCV transmission in pregnancy.
- More data are needed on safe combination HCV therapy for use in pregnancy and in young children

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