Intracellular Sofosbuvir Concentrations in Pregnant Women With Hepatitis C Virus

00710

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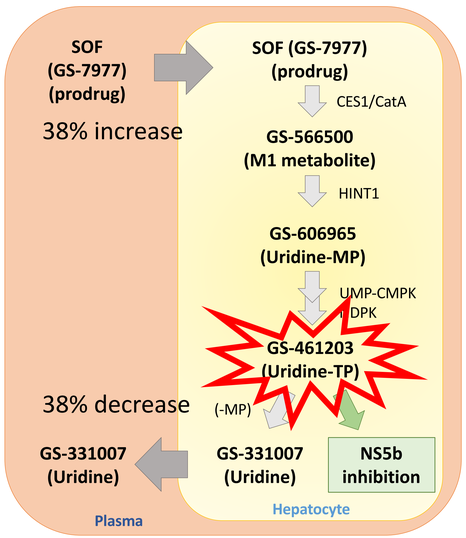
BACKGROUND

- Treatment of hepatitis C virus (HCV) during pregnancy could cure maternal HCV during antenatal care engagement and prevent perinatal HCV transmission[1].
- Plasma sofosbuvir (SOF) prodrug exposures were 38% higher and the inactive metabolite of SOF (GS-331007) was 38% lower in pregnancy[2].
- SOF is converted into its active form GS-461203 (Uridine-TP or 007-TP) within cells[3] such as red blood cells (RBCs) and peripheral blood mononuclear cells (PBMCs). These can be used as a surrogate of drug activation in other tissue types and adherence to SOF-containing regimens[4].

Figure 1. Pharmacology of SOF and 007



Key: CatA = cathepsin A, CES1 = carboxylesterase 1, HINT1 = histidine triad nucleotide binding protein 1; MP = monophosphate; NDPK = nucleoside-diphosphate kinase; SOF = sofosbuvir; TP = triphosphate (active metabolite); UMP-CMPK = uridine monophosphate/cytidine monophosphate kinase

- Our objectives were to describe 007-TP concentrations in dried blood spots (DBS) and peripheral blood mononuclear cells (PBMCs) during pregnancy.

METHODS

- In this open-label, phase 1 study, HIV-negative pregnant women with chronic HCV infection were treated with SOF 400mg/velpatasvir (VEL) 100mg daily starting at 23-25 weeks'.
- DBS and PBMCs were collected pre-dose at 3, 6 and 9 weeks.
- 007-TP in DBS (1x7mm punch) and PBMCs (normalized to 10^6 cells) were measured using validated LC/MS-MS methods[5].
- Results were summarized using descriptive statistics and compared to non-pregnant persons.

In comparison to non-pregnant adults, concentrations of the active metabolite of sofosbuvir in PBMCs were comparable or higher, whereas 007-TP in DBS were ~50% lower in pregnancy. All participants were cured.

RESULTS

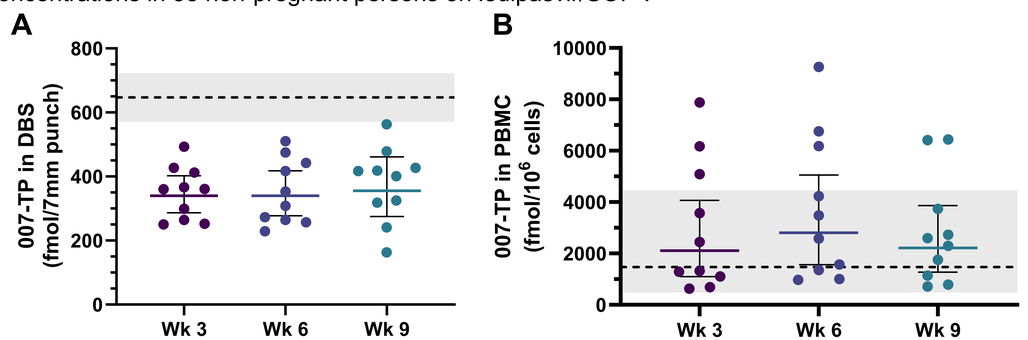
Data were available for 10 participants.

Characteristics	Number (%) or Median (range)
Age	31 (25, 39)
White Race	9 (90%)
Black Race	1 (10%)
Serum creatinine (mg/dL)	0.5 (0.4-0.6)
Glomerular Filtration Rate (mL/min/1.73m^2)	126 (122, 141)
Hematocrit (%)	36.1 (33.2-37.8)

Geometric Mean (95% CI) 007-TP Concentrations in DBS and PBMCs during SOF/VEL treatment in pregnant women with HCV

Time on Treatment	DBS (fmol/punch)	PBMC (fmol/10^6 cells)
3 weeks	340 (287, 403)	2111 (1096, 4066)
6 weeks	340 (278, 418)	2808 (1559, 5058)
9 weeks	356 (275, 461)	2212 (1267, 3864)

007-TP Concentrations in DBS (A) and PBMCs (B) during SOF/VEL treatment in pregnant women.
Data presented as geometric mean (95% CI). Dotted lines with gray shading reflect mean (95% CI) concentrations in 58 non-pregnant persons on ledipasvir/SOF[4].



In comparison to non-pregnant adults, 007-TP concentrations in PBMCs were comparable or higher, whereas 007-TP in DBS were ~50% lower in pregnancy.

CONCLUSIONS

- Though 007-TP concentrations were altered in pregnancy, the efficacy of SOF/VEL in this trial was unaffected (100% of those that attended the final maternal visit were cured [n=8]), which has previously been described with tenofovir-DP[6].
- The decreased concentrations in DBS could be due in part to physiologic hemodilution of pregnancy. Thus, if DBS samples were used to measure adherence in trials, they would need to be adjusted.
- **These PK results support the ongoing safety and efficacy evaluation of SOF/VEL treatment in pregnancy which is underway (NCT05140941).**

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