Direct-acting Antivirals [DAA] are Effective as Sole Treatment of Porphyria Cutanea Tarda [PCT] with Chronic Hepatitis C [CHC]

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RARE DISEASES CLINICAL RESEARCH NETWORK

The Porphyrias Consortium

Introduction

- CHC is a risk factor for PCT.
- Rx of PCT has usually been with iron reduction or low dose [hydroxy]chloroquine; then Rx of HCV.
- Recent case reports suggest that the newly available and highly efficacious DAA alone can both cure CHC and lead to remission of PCT. However, numbers of subjects studied have been small, and follow-up times have been short.
- PCT is well-known to be a relapsing disease.

Aims

- To treat patients with CHC+PCT with ledipasvir/sofosbuvir [Harvoni] and
- To follow them for ≥1 y to assess cure of CHC and prolonged remission of PCT.

Methods

- To be eligible for study, subjects were required to have documented chronic HCV due to genotypes, for which Harvoni is an FDA-approved treatment. Duration of treatment [12 or 24 weeks] depended upon the stage of liver disease at baseline, as assessed by Fibroscan [at Wake Forest] or Fibrometer [at UTMB, where Fibroscan was not available].
- We measured plasma and urinary porphyrins at baseline and monthly for the first 12 months and, whenever possible, at 16, 20, and 24 mos. All assays for porphyrins and their precursors were performed in the academic laboratory of Dr. Anderson at UTMB, Galveston, TX.
- We measured liver tests, CBC, and other routine lab studies, as well as HCV RNA in serum at baseline, end-of-treatment, 8-12, and 20-24 mos. All assays were performed at the Covance Central Laboratory, Indianapolis, IN.
- **Cure of HCV** was defined as no detectable HCV RNA in serum ≥ 3 months after end-of-treatment [EOT].
- **Clinical improvement in PCT** was assessed by skin exams for new PCT lesions.
- **Biochemical Remission of PCT** was defined as normalization of plasma and urinary total porphyrins [< 0.9 mcg/dL and < 226 mcg/g creatinine, respectively] and normalization of porphyrin profile [< 41% uro-+ heptacarboxyl-porphyrins] by HPLC.

Results

- We enrolled 15 previously untreated patients, 13 M, all with HCV genotype 1. 14 were White; 1 was Black.
- Mean age was 58.9 y.
- At baseline, HCV RNA in serum ranged from 0.26-4.32 x 10^6 IU/mL; and Metavir fibrosis scores, by Fibroscan or Fibrometer, were F1 [2], F2 [5], F3 [3], and F4 [2], not done in 3.
- At baseline, 7/15 had elevated serum ferritin suggesting iron overload; 10 regular alcohol use; 12 had current and 3 prior tobacco use.
- 1 had a genetic defect in UROD [familial PCT type 2].
- Selected other features are shown in Table 1.

Table 1. Selected Baseline Demographic and Laboratory Features of Subjects Studied

Subj #		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Demographics																
Age [y]		58.4	60.4	54.9	55.9	51.8	65.3	60.8	58.3	56.3	62.8	70.1	57.7	60.7	51.9	57.9
M/F		M	M	F	M	M	M	M	M	M	F	M	M	M	M	M
Lab Values	**Ref ranges**															
HCV RNA [IU/mL] x10^{-6}	0.0	4.32	0.22	2.09	0.91	6.32	8.29	1.38	13.5	2.76	1.56	0.90	0.025	0.64	0.28	0.77
ALT [U/L]	6-43	32	64	45	34	67	47	106	96	85	119	49	78	144	63	165
AST [U/L]	11-36	28	79	64	45	80	61	190	115	57	81	38	83	86	101	211
AP [U/L]	35-125	92	100	106	68	79	62	146	91	121	152	106	85	16	93	102
TBR [umol/L]	3-21	9	9	3	5	7	5	21	12	7	26	7	9	14	3	9
Albumin [g/dL]	3.3- 4.9	3.9	4.4	4.1	4.6	4.5	4.1	3.4	3.9	4.6	3.7	4.9	4.1	3.7	4.0	3.9
INR	0.8-1.2	1	1	1	1	1	1	1.1	1.2	1	1.1	0.9	1	1.1	1	1
Hgb [g/dL]	12-16	14.7	16.2	13.7	15.5	16.3	13.4	14.5	15.1	16.8	14.9	15.4	17.8	16.4	14.5	16.6
WBC [#/uL] x10^{-3}	3.8-10.8	6.46	7.24	9.59	10.47	7.47	6.87	8.81	9.4	5.91	8.06	8.84	6.39	6.16	7.08	6.29
Plat [#/uL]x10^{-3}	140-400	203	168	250	269	172	146	246	199	191	112	221	205	206	314	181

Fig 1. Time Course of Plasma total porphyrins [mcg/dL]. A. Spaghetti plot of all subjects; B. Mean values [+/- SE]. ULN is 0.9 mcg/dL [solid horizontal line]

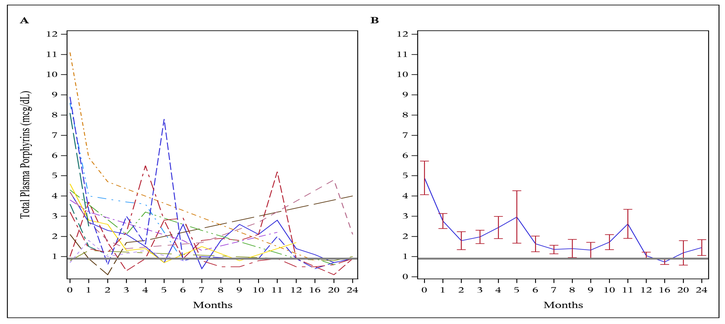
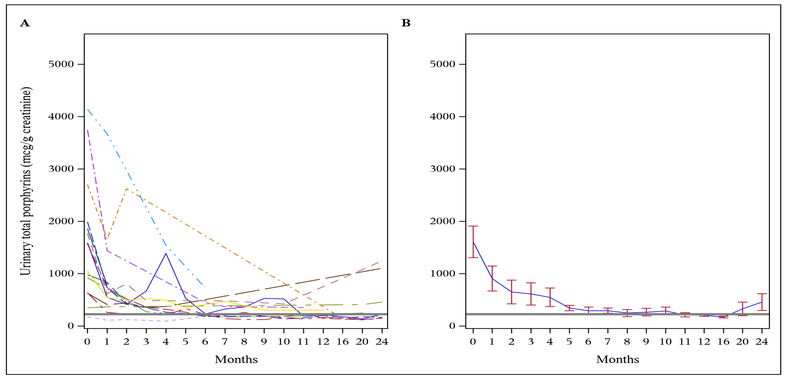


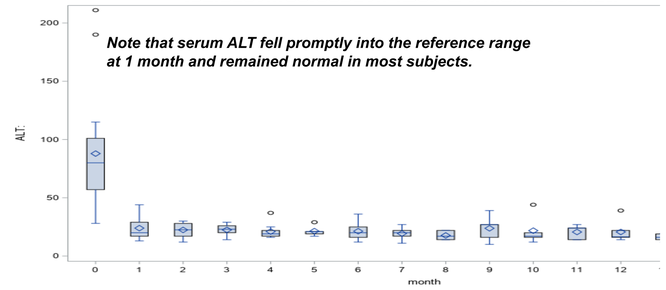
Fig 2. Urinary total porphyrins [mcg/g creatinine]. A. Spaghetti plots of all subjects; B. Mean values [+/- SE] ULN is 226 mcg/ g creatinine [solid horizontal line]



Note the progressive decreases in plasma and urinary porphyrins during 6-12 months of Harvoni, which persisted for 24 months, at least.

Results

Fig 5. Time course of Serum ALT [U/L]during and after treatment with ledipasvir/sofosbuvir [Box & whisker format]



- **Summary:** 13/15 completed the study; 2 failed to return and were lost to follow-up. 11/13 who completed the study were cured of CHC and achieved clinical remission & biochemical improvement of PCT [no new blisters or bullae; decreased plasma & urinary total porphyrins].
- 1 man had a complete clinical & virological response at EOT, followed by a low level of virological relapse. We treated him with Epclusa for 12 weeks with permanent cure of HCV. He continues to show clinical remission of PCT, albeit with an abnormal PCT-like pattern of urinary porphyrins. The other man, not cured after Harvoni, has active PCT & HCV; he chose to be re-treated elsewhere and has not returned to assess response. Both continued alcohol and tobacco use.
- ***The other subjects who completed treatment and follow-up all achieved cure of CHC and are in clinical remission and biochemical amelioration of PCT.***

Conclusions

- Ledipasvir/sofosbuvir [Harvoni] and sofosbuvir/velpatasvir [Epclusa], and likely other highly active DAA are effective treatment of both HCV and PCT, even in the presence of continuing alcohol use and/or iron overload.
- We recommend initial treatment of HCV + PCT with DAA alone.
- Treatment with iron reduction, usually by therapeutic phlebotomies, should be reserved for patients who also have iron overload, such as due to hemochromatosis.
- Treatment with low-dose [hydroxy] chloroquine should be reserved for the rare patients not cured of HCV and with persisting clinically active PCT.
- PCT does not decrease DAA efficacy to cure HCV.

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***see abstract book for full disclosures**