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Hepatitis C Treatment in Patients with Porphyria Cutanea Tarda

Ashwani K Singal, MD,
Division of Gastroenterology and Hepatology, UAB, Birmingham AL, USA

Krishna V Lakshmi, MD,
Department of Internal Medicine, UAB, Montgomery, AL, USA

Sarat Jampana, MD,
Department of Internal Medicine, University of Texas Medical Branch, Galveston TX, USA

Fakhar-Ul-Islam, MBBS*, and
Division of Gastroenterology and Hepatology, UAB, Birmingham AL, USA

Karl E Anderson, MD
Departments of Preventive Medicine and Community Health and Internal Medicine (Division of Gastroenterology and Hepatology), University of Texas Medical Branch, Galveston, TX, USA

Abstract

Background and Aim—Hepatitis C virus (HCV) infection is a common susceptibility factor for porphyria cutanea tarda (PCT). Experience on HCV treatment in PCT patients is limited. Recently, HCV treatment has improved with direct acting antivirals (DAA). We review our experience on HCV treatment in PCT patients with older and newer regimens.

Methods—HCV treatment was attempted 22 times in 13 PCT patients (five attempts in one, two in 5 and one in the other 7 patients).

Results—Before starting HCV treatment, PCT was in complete remission in 16, partial remission in 2, unknown status in 2, and active in 2 instances. PCT relapsed during therapy 6 times (all interferon based regimens, 2 including telaprevir), four requiring treatment interruption. Treatment was interrupted for reasons other than PCT relapse in 2 patients treated with interferon based regimens. To prevent PCT recurrence, HCQ was continued during HCV therapy 6 times (3 interferon regimens, 2 ribavirin regimens without interferon, and one DAA alone). Twelve patients achieved sustained viral response (SVR), 3 with interferon regimens and 9 with DAA. Two patients with active PCT were treated with DAA, with reduction of plasma porphyrins in one and normalization in the other at the end of HCV therapy.

Address for correspondence: Ashwani K. Singalm, MD, MS, FACG, Division of Gastroenterology and Hepatology | University of Alabama at Birmingham, 1808 7th Ave South, BDB 351 | Birmingham, AL 35294-0012, Ph: 205-934-5623 | Fax: 205-975-6201 | Call center: 205-996-4744, aksingal@uab.edu | ashwanisingal.com@gmail.com.
*Current Address: Aga Khan University Medical College, Karachi, Pakistan

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Conclusion—HCV treatment regimens including interferon or ribavirin may precipitate PCT relapse. HCQ may be useful to prevent such relapses. In this limited experience, DAA were not associated with PCT relapse. Studies are needed to examine DAA as primary PCT treatment in HCV-infected patients.

Keywords

Porphyria; Hepatitis C; DAA; Interferon

INTRODUCTION

Porphyria cutanea tarda (PCT) is the most common human porphyria and is due to deficiency of uroporphyrinogen decarboxylase (UROD) activity in hepatocytes.[1, 2] This enzyme deficiency results from an inhibitor that is generated in the presence of oxidative stress and mild to moderately increased amounts of hepatic iron.[1, 3, 4] Susceptibility factors for PCT include alcohol use, smoking, hepatitis C virus (HCV) infection, hemochromatosis gene (HFE) mutations, estrogen use, human immunodeficiency virus infection, and inherited UROD mutations.[1, 2, 5–9] PCT causes chronic cutaneous photosensitivity with blistering skin lesions on sun exposed areas. It is readily treatable either by repeated phlebotomy, which removes hepatic iron, or a low dose regimen of hydroxychloroquine (HCQ), which removes accumulated porphyrins from the liver,[7] and probably from other tissues.

HCV infection, which increases oxidative stress in hepatocytes and suppresses hepcidin production, thereby increasing iron absorption, is associated with 50–70% of PCT cases in the US.[1, 5–7] [10, 11] There are no current guidelines regarding treatment of HCV infection when associated with PCT. PCT is generally more symptomatic and needs treatment more urgently. Until recently, treatment of hepatitis C has been difficult and prolonged and not always successful, whereas treatment of PCT is virtually always effective. Further, response to interferon based therapy for hepatitis C is better after reduction of hepatic iron,[12, 13] which is almost always elevated with active PCT. Therefore, it is generally advised to treat and achieve remission of PCT and then attempt to treat HCV infection.[1, 14] But with the advent of newer direct-acting antiviral agents (DAA), HCV treatment has become more rapid, effective and safe.[15] However, there is little published experience with any treatments for hepatitis C in patients with PCT.

MATERIAL AND METHODS

We describe 13 patients with PCT who were selected because they underwent treatment for chronic hepatitis C after or before treatment of PCT. They underwent a total of 22 treatment courses for hepatitis C. Ten cases were treated at UTMB and 3 at UAB. Their clinical features, susceptibility factors, and porphyrin levels are summarized in Table 1, and details of each hepatitis C treatment regimen in Table 2 in the order of their first treatment for hepatitis C. These patients would be classified as type 1 (sporadic) PCT, because DNA studies showed that none had heterozygous UROD mutations [as found in type 2 (familial) PCT], and none had a family history of the disease in the absence of a UROD mutation (as

in type 3 PCT). However, response to hepatitis C treatment is not expected to be affected by the presence of a UROD mutation.

Case 1

This white male developed PCT at age 45 and was effectively treated elsewhere with a total of 8 phlebotomies. He also was found to have HCV genotype 1b infection at that time. Other PCT susceptibility factors were alcohol use, smoking, a heterozygous C282Y mutation of the HFE gene and iron overload (serum ferritin of 1471 ng/mL). He then failed three interferon plus ribavirin regimens elsewhere. After the second treatment attempt, PCT relapsed with a plasma porphyrin of 10.3 mcg/dL and ferritin of 211 ng/mL, which was treated successfully by phlebotomy. The third was an investigational high dose pegylated interferon (PEGIFN) plus ribavirin regimen that caused pancytopenia, weight loss and a recurrence of PCT, with a plasma porphyrin level of 11.8 mcg/dL and serum ferritin of 245 ng/mL. After this unsuccessful course of HCV treatment, he was enrolled in a PCT treatment study and achieved remission of PCT with low dose HCQ 100 mg twice weekly. HCQ was then continued during an unsuccessful investigational treatment with IL-29 and ribavirin, and then also during a successful trial with a DAA elsewhere. HCQ was stopped after he achieved SVR, and PCT has remained in remission for five years.

Case 2

This white female developed PCT at the age of 42, and was also found to have genotype 1 HCV infection acquired from previous IV drug abuse. Other PCT susceptibility factors included smoking (53 pack years) and alcohol use (half gallon of whiskey per day for 29 years). She had blisters and crusted lesions on the back of her hands, lower forearms, face, and feet. Laboratory findings included HCV RNA 479,015 IU/mL, serum ferritin 201 ng/mL, plasma porphyrins 25.5 mcg/dL, and urine porphyrins 9,703 nmol/L with a predominance of highly carboxylated porphyrins (Table 2). Liver biopsy showed bridging fibrosis (stage 3 disease) without steatosis or excess iron.

She was treated with HCQ 100 mg twice a week as a participant in a study comparing this treatment with phlebotomy. After achieving remission of PCT, she was started on PEGIFN and ribavirin for treating HCV infection. An early virologic response occurred at 3 months, but she developed blistering skin lesions with elevated plasma porphyrins of 19.2 mcg/dl and urinary porphyrins of 8,997 nmol/L (36% uroporphyrin, 50% heptacarboxyl porphyrin, 4% hexacarboxylporphyrin, 3% pentacarboxylporphyrin, and 6% coproporphyrin. She remained abstinent of smoking and of alcohol use since beginning of treatment. She was hospitalized with pneumonia and pancytopenia (presumably due to PEG interferon) and HCV treatment was interrupted. After recovery from pneumonia, low-dose HCQ was started for PCT. Once PCT was in remission, the same HCV treatment was restarted and continued along with low dose HCQ for 1 year. A sustained viral response (SVR) was achieved and PCT has remained in remission for 6 years. On follow up after SVR, she remains abstinent of alcohol use but resumed smoking intermittently.

Case 3

This white female with a history of intravenous drug use was diagnosed with both PCT and chronic HCV infection genotype 1b at age 52, after she developed blisters on the dorsal hands, face, arms and feet. Other susceptibility factors for PCT were alcohol use (about 9 drinks per week), smoking 1 packs per day since age 23, oral contraceptive use before hysterectomy at age 36 and replacement estrogen use after age 50. She was treated with low-dose HCQ treatment until plasma porphyrins were normal. HCQ was then continued during HCV treatment with PEG interferon and ribavirin. She achieved SVR and PCT has also remained in remission for four years.

Case 4

This white female developed PCT at age 49 and was simultaneously found to have chronic HCV infection genotype 1a. PCT was treated successfully by repeated phlebotomy. Other susceptibility factors for PCT were absent. Hepatitis C was treated with PEGIFN and ribavirin at age 51, but was stopped after two months due to lack of response and relapse of PCT. At age 63 she was treated with sofosbuvir and simeprevir for 12 weeks without adverse effects or relapse of PCT. At the end of treatment HCV RNA was undetectable and urine and plasma porphyrins were normal (132 nmol/L and 0.2 mcg/dL, respectively) and have remained so for two years.

Case 5

This white male with a history of excess use of alcohol developed PCT at age 54, with blistering lesions on the dorsal hands. He was also found to have chronic HCV genotype 1b infection. Remission of PCT was achieved after 7 biweekly phlebotomies of 450 mL each. At age 58 HCV treatment with PEG interferon and ribavirin was initiated. However, this was discontinued due to fatigue, thrombocytopenia, and depression. At age 64, PCT was in remission (urine and plasma porphyrins of 42 nmol/L and 0.1 mcg/dL respectively) and there was no evidence of cirrhosis by clinical, biochemical, and liver imaging evaluation. Treatment with sofosbuvir and simeprevir for 12 weeks achieved SVR, and PCT has remained in remission for two years.

Case 6

This white male with a history of intravenous drug use developed PCT at age 43, when he presented with skin blisters and friability on the dorsal hands. Susceptibility factors for PCT included chronic HCV infection (genotype 1b), heavy alcohol use, and a heterozygous H63D mutation of the HFE gene. PCT was treated successfully by phlebotomies and he abstained from alcohol use. He resumed drinking 4–5 drinks per week from age 48 to 53, and then stopped again. Several recurrences of PCT, the last at age 53, were treated by phlebotomy. Liver biopsies at ages 43 and 48 showed stage 1 fibrosis, and a repeat biopsy at age 53 showed stage 3 fibrosis. He started therapy for hepatitis C at age 54 with PEGIFN, ribavirin, and telaprevir. He responded well with undetectable HCV RNA after 4 weeks of therapy. However, development of migraine and pancytopenia required dose reduction and transfusion with 2 units of packed red blood cells. HCV relapsed and PCT recurred, with ferritin levels exceeding 1,000 ng/mL. PCT was retreated with phlebotomy. At age 57 he

was retreated for hepatitis C with sofosbuvir and simeprevir for 12 weeks, with no side effects. HCVRNA remains undetectable and PCT remains in remission, with normal urine and plasma porphyrins for over one year.

Case 7

At the age of 48 years, this white male with a history of past intravenous drug use, developed PCT with blisters and increased fragility on the dorsal hands and face. He was also found to have chronic HCV genotype 1a infection. PCT was treated by repeated phlebotomy, which achieved the target ferritin of <20 ng/mL, and urine and plasma porphyrin concentrations became normal. He was then treated with sofosbuvir and ledispavir for 24 weeks. He developed SVR and PCT has not relapsed during one year of follow up.

Case 8

This white male developed friable skin and blisters on the dorsal hands and fingers at age 46, which worsened gradually. He was found to have PCT as well as chronic HCV infection (genotype 1) at age 48. He drank about 15 drinks daily from age 19, and reduced to about 1 drink daily at age 48, smoked about 10 cigarettes daily since age 17, and was heterozygous for the H63D mutation of the HFE gene. PCT was treated with low-dose hydroxychloroquine 100 mg twice weekly for 21 months, and his lesions cleared and did not recur. At age 49 he was continued on HCQ to prevent recurrence of PCT during treatment with PEGIFN and ribavirin. HCV RNA remains undetectable and PCT in remission after 5 years.

Case 9

This white male with a history of intravenous drug use, heavy alcohol use, and smoking was found to have hepatitis C (genotype 2b) at age 49. At age 59 he developed blisters, increased friability and milia that progressively worsened on the dorsal hands and right forearm. He stopped alcohol but continued to smoke 1 pack per day, was heterozygous for the H63D mutation of the HFE gene, and was taking carisoprodol for chronic musculoskeletal pain. Treatment with low dose HCQ achieved remission of PCT. HCQ was continued during HCV treatment with sofosbuvir and ribavirin for 12 weeks. Six months after treatment, HCVRNA was undetectable and PCT also remains in remission.

Case 10

This African American male with a history of jaundice at age 7 and heavy alcohol intake (750 mL per day from age 20 until he stopped at age 62) and a 1 pack per day history of smoking, noted friability of the skin on the dorsal hands beginning at age 55. At age 62 he was started on triple therapy (teleprevir, PEG interferon and ribavirin) for genotype 2b HCV infection. Hepatitis B surface antigen was positive, but hepatitis B virus DNA was negative. He developed progressively worsening side effects including severe fatigue, shortness of breath, insomnia, decreased appetite, headaches, dizziness and balance problems, and pancytopenia. Therefore, treatment was stopped after 16 weeks, at which time HCVRNA was undetectable. He developed blisters on the dorsal hands at 1 month after stopping therapy, and at 6 months HCV was found to have relapsed. PCT relapse was treated with low

dose HCQ (100 mg twice weekly), to which he was noncompliant. At age 64 he completed 12 weeks treatment with sofosbuvir and simeprevir. HCVRNA was undetectable at 8 and 12 weeks after starting therapy, before he was lost to follow up.

Case 11

This white male developed PCT at age 48 with blisters on the dorsal hands. He was known to have chronic hepatitis C (genotype 1) for many years acquired from intravenous drug use. He was treated elsewhere by phlebotomy and the blisters resolved. PCT relapsed on 5 different occasions, treated successfully each time by phlebotomy. He decreased use of alcohol from about 12 to 3 beers daily, and continued to smoke a half pack of cigarettes per day since age 16. At age 59, when he had mild blistering on the dorsal hands, he was treated with sofosbuvir and ledispavir for a total duration of 12 weeks. He achieved SVR and PCT resolved and has remained in remission for more than 1 year.

Case 12

This white male was found to have HCV infection (genotype 4) at age of 60 and was treated unsuccessfully with PEG interferon and ribavirin, which was discontinued after 6 months due to poor tolerance and anemia. A liver biopsy at age 66 years showed cirrhosis. At age 67 he first developed blistering skin lesions on the dorsal hands, with elevated urine porphyrins at 2,623 nmol/L (uroporphyrin 52%, heptacarboxyl porphyrin 31%, hexacarboxyl porphyrins 5%, pentacarboxyl porphyrins 7%, and coproporphyins 5%) and plasma porphyrins of 5.2 mcg/dL. The level of HCVRNA was >10 million copies/mL. After completing 24 weeks of treatment with sofosbuvir and ledispavir a SVR was achieved. Skin lesions resolved during treatment and plasma porphyrins have so far decreased to 2.3 mcg/dL.

Case 13

This white male was found at age 48 to have chronic HCV infection (genotype 3a), acquired previously from intravenous drug use. Other susceptibility factors for PCT included heavy alcohol use and smoking. At age 51 he developed blistering on the dorsal hands, and later on the scalp and feet. He improved several times without treatment when he stopped drinking. He has been abstinent since age 62, but continues to smoke. He avoided sunlight and had no blisters after age 63, although urine and plasma porphyrins remained mildly elevated, with a predominance of uroporphyrin and heptacarboxyl porphyrin. Ultrasound showed coarsened hepatic echotexture without splenomegaly, and liver biopsy showed bridging fibrosis. He was treated with sofosbuvir, daclatasvir and ribavirin at age 64. Although treatment was shortened to 10 weeks due to a severe rash, SVR and normal porphyrin levels were achieved, and persist after 6 months.

DISCUSSION

These 13 cases of PCT associated with chronic HCV infection as well as other coexisting susceptibility factors were managed before and during a period when treatment of chronic hepatitis C is improving dramatically. In the era of interferon treatment of hepatitis C, it has been traditional to treat PCT first and hepatitis C later, not only because PCT is generally

more symptomatic and readily treated, but the treatment duration was shorter with a better response rate and fewer side effects.[1,][14] In addition, response to interferon based therapies was reported to be better after reduction of iron overload by phlebotomy.[12] In this case series of 13 patients, we describe effects and interactions of treatments for these two conditions. Four courses of interferon and ribavirin based therapy in 3 patients were associated with recurrence of PCT, as observed in earlier reports.[16–19] Ribavirin can cause hemolytic anemia which may reduce hepcidin levels and lead to increased iron absorption and contribute to hepatic iron overload,[20, 21] and interferon may increase oxidative stress in hepatocytes, resulting in increased generation of UROD inhibitor.

Low-dose HCQ was successful in preventing recurrence of PCT during 5 courses of HCV therapy (all including ribavirin and 3 including interferon) that achieved sustained viral responses. This treatment combination has, to our knowledge, not been previously reported to be useful in patients with both conditions, and warrants further study for confirmation. Use of phlebotomies to prevent recurrence of PCT during regimens including interferon or ribavirin is likely to be problematic because these agents often cause anemia. Although in the future these regimens are likely to be used less often than DAA for treating hepatitis C, cost considerations may favor their use particularly in treating certain HCV genotypes.

The newer DAA based regimens for treatment of HCV are shorter, safer and much more effective than interferon based regimens, with SVR rates of over 95%.[15] Therefore, initial treatment of both HCV and PCT with a DAA based regimen is appealing. In one reported case, remission of PCT was achieved with boceprevir based triple therapy.[22] In this series, two patients were treated for HCV using DAA when the PCT was active, and porphyrins decreased significantly in one patient and completely normalized in the other. Susceptibility factors in addition to hepatitis C are almost always identifiable in these patients,[6] as in all but one patient in this series. Given the heterogeneity of susceptibility factors, it remains unclear how often cure of HCV infection will lead to remission of PCT, and whether remission is achieved as rapidly as with phlebotomy or low dose HCQ.

Strengths of this report include a large number of patients with well-documented PCT who were observed as carefully as possible to document remission of both PCT and hepatitis C. A limitation is that the patients were not in a study to assess treatment of hepatitis C, although most participated in a study comparing time to remission with HCQ or phlebotomy.[7] By chance, none of the patients had heterozygous UROD mutations, but it is unlikely that the presence of this susceptibility factor would alter response to treatment of hepatitis C.

CONCLUSIONS AND REFERENCES

Our experience demonstrates a) that treatment regimens that includes PEGIFN and ribavirin, which remain important in economically disadvantaged countries, can worsen PCT or be associated with the onset of PCT, b) continuing low dose HCQ treatment may be a good option for preventing worsening of PCT during such regimens, c) based on limited experience, DAA based HCV therapy may not be associated with onset or worsening of PCT, and d) treatment with DDAs may be as safe and effective as primary treatment for

PCT, when associated with hepatitis C. But treatment of PCT by phlebotomy or low dose HCQ remain highly effective and with comparable times to remission.[7] Therefore, further studies, such as those initiated by the Porphyrias Consortium, are needed to establish whether effectiveness and time to remission of PCT with DAA treatment is non-inferior to and as durable as with phlebotomy or low dose HCQ.

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Table 1

Clinical features, susceptibility factors and initial plasma and urine porphyrin levels in 13 patients with hepatitis C and porphyria cutanea tarda as documented by excretion of mostly highly carboxylated porphyrins (uroporphyrin and heptacarboxyl porphyrin)

	Age at onset of PCT (years)	Sex	HCV genotype	Alcohol use	Smoking	HFE genotype	Plasma porphyrins (ug/dL)	Total urine porphyrins (nmol/L)	Uroporphyrin and heptacarboxyl porphyrin (percent of total)
1	45	M	1b	+	+	C282Y/WT	10.3	4100	68, 24
2	42	F	1b	+	+	C282Y/WT	25.5	9703	33, 17
3	52	F	1b	+	+	WT/WT	4.7	2724	47, 46
4	49	F	1a	−	−	WT/WT	0.1	114	Not done
5	54	M	1b	+	−	WT/WT	0.1	42	Not done
6	43	M	1b	+	−	H63D/WT	2.0	822	21, 36
7	48	M	1a	−	−	WT/WT	10	4737	38, 31
8	46	M	1	+	+	H63D/WT	2.4	1676	41, 46
9	49	M	2b	+	+	H63D/WT	2.8	2375	61, 30
10	55	M	2b	+	+	WT/WT	7.2	4905	64, 27
11	48	M	1	+	+	WT/WT	2.3	662	52, 27
12	67	M	4	−	+	Not available	5.2	2623	52, 31
13	51	M	3a	+	+	WT/WT	4.3	932	40, 26

Abbreviations: PCT: porphyria cutanea tarda; WT: Wild type; HCV: Hepatitis C virus

Reference ranges: plasma porphyrins, <0.9 mcg/dL; total urine porphyrins <300 nmol/L; uroporphyrin and heptacarboxyl porphyrin, <30 and <5 percent of the total, respectively.

Table 2

Hepatitis C treatment details in 22 instances in 13 patients with porphyria cutanea tarda

Case	Age when treated (years)	PCT status before treatment	HCV regimen	PCT relapse during or after treatment	Treatment interruption	HCQ during treatment	SVR
1	45	Remission	PEGIFN+ribavirin	No	No	No	No
	46	Remission	PEGIFN+ribavirin	After	No	No	No
	47	Remission	PEGIFN+ribavirin	During	No	No	No
	48	Remission	IL-29 + ribavirin	No	No	Yes	No
	50	Remission	DAA	No	No	Yes	Yes
2	51	Remission	PEGIFN+ribavirin	During	Yes	Yes	Yes
3	53	Remission	PEGIFN+ribavirin	No	No	Yes	Yes
4	51	Remission	PEGIFN+ribavirin	During	Yes	No	No
	63	Remission	Sof+Sim	No	No	No	Yes
5	58	Remission	PEGIFN+ribavirin	No	Yes	No	No
	64	Remission	Sof+Sim	No	No	No	Yes
6	54	Partial remission	PEGIFN+ribavirin+telaprevir	After	Dose reduction	No	No
	57	Remission	Sof+Sim	No	No	No	Yes
7	48	Remission	Sof+Led	No	No	No	No
8	46	Remission	PEGIFN+ribavirin	No	No	Yes	Yes
9	59	Remission	Sof+ribavirin	No	No	Yes	Yes
10	62	Not available	PEGIFN+ribavirin+telaprevir	After	Yes	No	No
	64	Unknown	Sof+Sim	No	No	No	No *
11	59	Partial	Sof+Led	No	No	No	Yes
12	60	Remission	PEGIFN+ribavirin	No	Yes	No	No
	67	Active	Sof+Led	No	No	No	Yes
13	63	Active	Sof+Dac+ribavirin	No	No	No	Yes

* Lost to follow up after documenting undetectable HCVRNA at end of treatment

Abbreviations: PCT, porphyria cutanea tarda; HCV, hepatitis C virus; PEGIFN: Pegylated interferon; SOF: Sofosbuvir; Sim: Simeprevir; Led: Ledipasvir; DAA, direct acting antiviral agent(s); SVR, sustained virologic response (defined as undetectable HCVRNA at 12–24 weeks after discontinuation of hepatitis C therapy)