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Management of Hepatitis C Virus in Patients with Porphyria Cutanea Tarda

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Extrahepatic manifestations associated with chronic hepatitis C virus (HCV) infection are increasingly recognized and often complicate HCV therapy. Porphyria cutanea tarda (PCT), an uncommon phenotypic expression of a defect in the uroporphyrinogen decarboxylase enzyme, is 12 times more likely to occur in those with HCV compared with the general population in the United States. It is hypothesized that increased free intrahepatic iron levels and chronic HCV infection can accelerate the pathogenesis of liver injury in patients with phenotypic expression of PCT. Symptomatic treatment of PCT has traditionally revolved around phlebotomy to control total body iron levels. However, phlebotomy for PCT management poses a challenge to concomitant treatment of HCV with combination therapy, ribavirin, and interferon. This article highlights the pathogenesis of PCT and discusses its impact on the management of HCV in individuals with this uncommon extrahepatic disease.

Introduction

Hepatitis C virus (HCV) has become a worldwide epidemic, with an estimated 170 million people infected [1••,2–4,5••]. In the United States, approximately 2% of the 295 million population currently have HCV antibodies. Of these 5 to 6 million people, approximately 74% will have a chronic HCV infection. Further, of those infected, 10% to 20% will eventually progress to hepatic fibrosis and cirrhosis [5••]. Despite the improved screening of blood products and decreased numbers of new infections, the number of active cases of HCV that are coming to light in the medical community continues to rise. This is occurring both as a result of increased numbers of patients undergoing routine blood work as well as the expression of clinically symptomatic cirrhosis.

Clinical Manifestations of HCV Infection

The initial inoculation with the HCV often goes undetected because infected adults rarely manifest overt symptoms of recent exposure. It is estimated that the incubation period averages from 6 to 7 weeks (range 2–26 weeks). In only 30% to 40% of those afflicted is the infection heralded by a mild case of the "flu" or other nonspecific viral illness [1••]. From this origin the disease most often progresses on an indolent course with nonspecific somatic complaints of fatigue, joint aches, abdominal pain, and pruritus. Chemical markers can consist of nonspecific fluctuating transaminases that are often the only indication of an underlying pathologic process. In those patients who are evaluated for their disease and undergo a liver biopsy, their histopathologic findings are acutely often difficult to distinguish from other hepatitis infections, with the possibility of a greater predominance of fatty changes. These histopathologic features, in an active noncirrhotic infection, include pleomorphism of hepatocytes, foci of lobular necrosis and inflammation, acidophilic and apoptotic bodies, and portal tract inflammation with piecemeal necrosis that eventually progresses to bridging fibrosis and cirrhosis.

It is estimated that 40% of individuals infected with HCV will develop one or more extrahepatic manifestations without evidence of overt liver injury or cirrhosis. These extrahepatic findings include, but are not exclusive to, diseases such as autoimmune thyroiditis, membranous glomerulonephritis, Hodgkin's and non-Hodgkin's lymphoma, cryoglobulinemia, Sjögren's syndrome, and porphyria cutanea tarda (PCT) (Table 1) [6,7].

The etiologies or mechanisms of how chronic HCV infection results in these processes are often unclear. In many it is thought to be autoimmune mediated in nature. It is speculated that the viral-dependent proliferation of monoclonal and polyclonal lymphocytes results in the deposition of immune complexes in a variety of organs. This deposition results in the activation of different immune-mediated cascades, resulting in the phenotypic expression of these disease processes [1••]. Other theories have suggested that it is direct involvement of the HCV on the afflicted organ system that manifests itself in these clinical entities via a number of different mechanisms. Overall, the spectrum of extrahepatic involvement is vast (Table 1), and in some instances the mechanism is understood, in others it is speculated, and in still others it is a complete mystery.

Table 1. Extrahepatic manifestations of HCV

Membranous and membranoproliferative glomerulonephritis
Adult-onset diabetes
Lichen planus
Vitiligo
Porphyria cutanea tarda
Essential mixed cryoglobulinemia
Autoimmune thyroiditis
Sjögren's syndrome
Arthritis
Cutaneous necrotizing vasculitis
Hyper- and hypothyroidism
Hashimoto's and autoantibody thyroiditis
Uveitis
Aplastic anemia
Peripheral neuropathy
Pruritus
Behçet's syndrome
Fatigue and muscle weakness

HCV—hepatitis C virus.
(*Data adapted from* Hadziyannis [6] and Agnello and De Rosa [7].)

PCT: Pathology and Clinical Presentation

Porphyria cutanea tarda is a cutaneous disease process associated with photosensitizing action on accumulated porphyrins in the skin. Porphyrin activation results in increased skin fragility, hypertrichosis of light exposed areas, chloracne, hyperpigmentation, sclerodermoid changes, dystrophic calcifications with ulcerations, scarring, alopecia, and onycholysis [1••,3,5••,8–10]. Traditionally, these findings are manifest clinically by the blisters, vesicles, and/or milia seen on the dorsal aspect of hands and other photoexposed areas.

The proposed mechanism of injury for this phenotypic expression is from the accumulation of uroporphyrin and other highly carboxylated porphyrins in the epidermis and their resultant photoactivation. As these oxidized metabolites diffuse from the plasma into the upper dermis, because of their water-soluble nature, they are exposed to photoactivation, creating reactive oxygen singlets that in turn form free radicals. These free radicals are then involved in the activation of the local compliment cascades, resulting in the splitting of the dermis through bullae formation in the subepidermal layer [11]. Bullae formation and resultant splitting is the phenotypic expression that identifies most patients as carriers of the genetic defect that reduces the activity of uroporphyrinogen decarboxylase (UROD).

Uroporphyrinogen decarboxylase is an enzyme that catalyzes the removal of the four carboxyl groups from the less soluble uroporphyrinogen in the heme biosynthesis pathway (Fig. 1). This allows for the conversion of the less soluble uroporphyrinogen into a more soluble and, thus, excretable form coproporphyrinogen. Under normal circumstances, the reduction of UROD activity by 50%, as

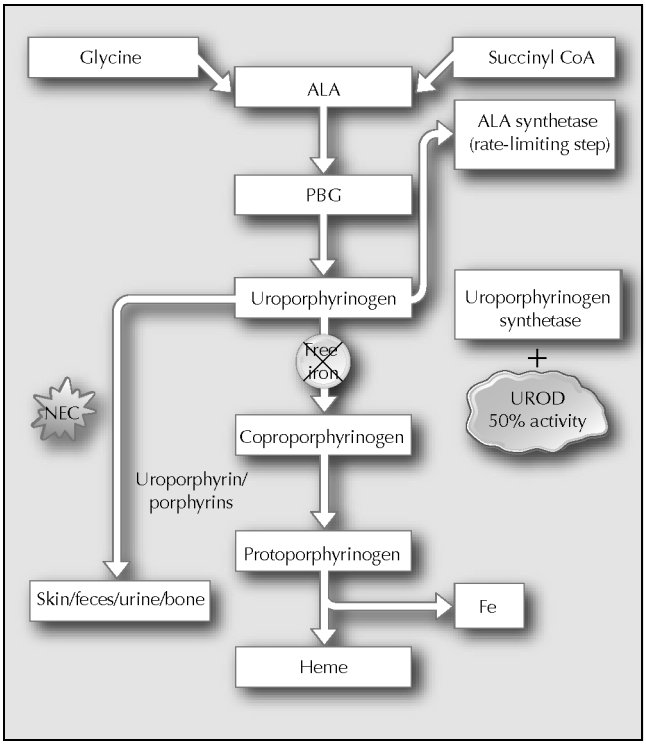

Figure 1. Heme biosynthesis and the mechanism of porphyria cutanea tarda. ALA—aminolevulinic acid; CoA—coenzyme A; Fe—iron; NEC—nonenzymatic cyclization; PBG—porphobilinogen; UROD—uroporphyrinogen decarboxylase.

found in the sporadic form, is still enough to retain the function needed to prevent the buildup of uroporphyrinogen that results in the phenotypic expression of PCT [1••]. However, given the appropriate setting, which includes such events as increased cytochrome P-450 activity, estrogen use (a cause of PCT in one quarter of all female patients with PCT), increased activity of aminolevulinic acid (the rate-limiting step in heme synthesis), and disease processes that result in the increased availability of metabolically active iron, such as seen with chronic hepatitis C, hemochromatosis (usually the subclinical form), and long-term alcohol abuse, there is a subsequent compounding of the reduced function of UROD in the heme biosynthesis pathway. This results in an accelerated inability to remove the requisite four carboxyl groups from uroporphyrinogen, and a resultant progression to the oxidized form uroporphyrin [1••,10,11–13]. Over time these oxidized porphyrins are allowed to leak out of the liver into the plasma as the intrahepatic storage reserves are overloaded. The porphyrins are then taken up into the peripheral tissues where they are deposited into skin, bones, and teeth. It is in the skin that photoactivation allows for phenotypic expression of an often otherwise unrecognized biochemical process and genetic defect.

Porphyria cutanea tarda has been subdivided into two basic subgroups depending on tissue involvement of the UROD deficiency. The first, known as familial (type 2 and 3), results in the generalized reduction of UROD in

Table 2. HCV prevalence in PCT by country

Study	Country	HCV prevalence, *n*	HCV, %
Stuart *et al.* [15]	Australia	7/26	26
Gibson *et al.* [16]	Australia	26/112	23
Martinelli *et al.* [17]	Brazil	15/23	65
Wolff *et al.* [18]	Chile	9/17	53
Malina *et al.* [19]	Czech Republic	20/92	22
Stransky *et al.* [20]	Czech Republic	14/66	21
Cribier *et al.* [21]	France	7/13	54
Dereure *et al.* [22]	France	20/36	56
Lamoril *et al.* [23]	France	18/65	28
Tannapfel *et al.* [24]	Germany	28/190	15
Murphy *et al.* [25]	Ireland	2/20	20
Andreone *et al.* [26]	Italy	8/9	89
Ferri *et al.* [27]	Italy	18/23	77
Fracanzani *et al.* [28]	Italy	48/53	90
Rivanera *et al.* [29]	Italy	34/40	83
Kondo *et al.* [30]	Japan	22/26	85
Siersema *et al.* [31]	Netherlands	7/38	18
Dabrowska *et al.* [32]	Poland	12/29	41
Carpentero *et al.* [33]	Spain	29/36	80
Herrero *et al.* [34]	Spain	75/100	75
Navas *et al.* [35]	Spain	21/32	65
Bonkovsky *et al.* [36]	USA	39/70	56
Egger *et al.* [37]	USA	29/39	74
Chuang *et al.* [38]	USA	16/17	94

HCV—hepatitis C virus; PCT—porphyria cutanea tarda.

all tissues. The second, also known as sporadic or type 1, results in a 50% reduction in UROD activity within the hepatocytes [11]. Of these two, the sporadic form of PCT is the more prevalent and is responsible for the genetic defect seen in approximately 75% of the total afflicted population, with the familial form making up the remaining 25% [1••].

Association of PCT and HCV

There are many disease processes that are speculated to propagate the phenotypic expression of sporadic PCT by some still poorly understood but hypothesized mechanisms. It is now relatively well established that there is a definitive link between HCV infection and PCT. The literature, although sparse on treatment options and mechanisms of injury in HCV-induced PCT, does repeatedly illustrate evidence that HCV infection is related to an increased phenotypic expression of PCT when compared with that seen in the general population. A retrospective study done by El-Serag *et al.* [14•] comparing the extrahepatic manifestations of HCV infection in 34,204 male U.S. veterans with HCV against 136,816 male U.S. non–HCV-infected control subjects found that the prevalence of PCT in the HCV population, although low at 0.77%, still had an odds ratio 12 times greater for phenotypic expression when compared with its prevalence in the control population, which was calculated at 0.06%. This association is reiterated in multiple independent studies done both in Europe and the United States that show a marked increase in the rate of HCV infection in patients with phenotypic expression of PCT when compared with the general population (Table 2) [15–38]. It is also suggested that the prevalence of HCV infection in phenotypic PCT is more complex and involved than was initially expected. This is illustrated in the wide variance of the percentage of patients with PCT in their coinfection with HCV based on geographic location.

On closer inspection of the epidemiologic data, it is also intriguing to note that the rate of HCV infection between sporadic and familial PCT dramatically differs [5••,9,39]. A retrospective analysis done by Lamoril *et al.* [9], looking at 124 patients from northern France with PCT between 1995 to 1997, found that the rate of infection with HCV was almost threefold higher in sporadic PCT versus the familial form (25.6% vs 9.7%, respectively). Another study done by Gisbert *et al.* [5••] provided a more global perspective by retrospectively comparing 50 studies from around the world. This provided for a cohort of 2167 PCT cases with concomitant HCV infection. In this meta-analysis, it was found that the rate of HCV infection in sporadic PCT was more than double that found in the familial form (57% compared with 26%, respectively), suggesting a causal rather than an independent relationship. As with Lamoril *et al.* [9], Gisbert *et al.* [5••] were unable to link differences in HCV genotype to a preferential phenotypic expression of PCT. Once again, a striking geographic variation in the prevalence of HCV infections in phenotypic PCT was observed. Despite this difference, it was still evident that there existed an increase in HCV infection rates in sporadic PCT across geographic boundaries, suggesting a possible etiopathogenic role of HCV in PCT.

In the United States, HCV infection is found in almost 60% of those patients with PCT, compared with the 2% prevalence in the general population [11]. HCV infection in patients with a genetic UROD deficiency is not only a risk for dermal manifestations, but there is mounting evidence that suggests that the concomitant HCV infection superimposed on PCT results in earlier liver dysfunction. This accelerated dysfunction not only manifests itself via earlier expression of phenotypic PCT when compared with non–HCV-infected patients with PCT, but it is also seen as worse histology on biopsy [11,39,40]. The link to earlier phenotypic expression in HCV-infected patients invariably leads back to an increase in hepatic porphyrin levels. This increase in porphyrin levels is also believed to have an increased carcinogenic effect, as demonstrated by a 15% prevalence of hepatocellular carcinoma development within a decade after phenotypic expression of PCT [11].

Although the exact mechanism of how HCV infection and PCT phenotypic expression are linked has not yet been established, there has been no evidence linking the two in a reverse fashion. PCT has not been shown to increase the likelihood of HCV infection [9]. At present, the most reasonable hypothesis set forth in the literature is that the phenotypic expression of PCT is not solely catalyzed by an HCV infection, but rather requires a combination of genetic, infectious, and environmental factors. HCV seems to provide an accelerating catalyst to this system by allowing the decompartmentalization of hepatocytic iron, giving rise to "free iron." This free iron in an oxidized form further inhibits the conversion of uroporphyrinogen to coproporphyrinogen by UROD allowing for uroporphyrinogen to undergo oxidation to uroporphyrin (Fig. 1) [41]. This resultant buildup of porphyrin, and eventual leakage out of the hepatocytes, results in an increase in plasma porphyrin levels. These are then transported to and absorbed by peripheral tissues, where they are photoactivated and phenotypic expression is observed.

Biochemical buildup of porphyrins and eventual leakage out of the overloaded hepatocytes into the periphery allows for the increased excretion in both the urine as well as feces of uroporphyrin, in both its original oxidized form as well as acetic acid–substituted porphyrin forms such as heptacarboxyporphyrin [1••,12,42]. The excretion of urinary porphyrin or fecal isocoporphyrins allows the clinician an indirect way to measure the extent of system saturation. Because the measurement of urinary porphyrins is easier and esthetically more appealing to the patient, a 24-hour urine can be used to estimate liver saturation.

At present, a urinary porphyrin level of more than 2 μmol per 24 hours suggests extensive liver accumulation and an increased risk of phenotypic expression [1••,12]. Other more invasive tests, such as liver biopsy with microscopic evaluation looking for the prevalence of intracellular porphyrins or long-wave ultraviolet light scans with resultant red fluorescence of biopsy tissues, also verify hepatic porphyrin overload. However, the efficacy of routine liver biopsies is probably not warranted given that the information from these modalities does not provide the clinician with sufficient increased data to justify the inherent risks of the procedure (*eg*, bleeding, infection, pneumothorax, and so forth) [1••,12,13,43•]. Further, there is no evidence that periodic liver biopsies for surveillance of liver injury in PCT has been shown to be of great benefit. An argument could be made that in the newly diagnosed patient with PCT a "staging" liver biopsy is warranted even though management is based on phenotypic resolution. This is because approximately 50% of the patients with PCT who were biopsied illustrate more severe disease than the expected stainable iron and fatty changes. These patients have progressed in their liver disease to lobular necrosis or inflamed fibrotic portal tracts, with up to 15% having changes consistent with cirrhosis [11].

Treatment of PCT

Although modifications to lifestyle habits, such as sun avoidance, long sleeve clothing, and ultraviolet protection via sun blocks, are used to help decrease the incidence of phenotypic PCT expression, the majority of effective treatment has focused on porphyrin reduction mainly through iron store modulation or depletion. The goal of therapy is to reduce total oxidized iron levels to prevent further inhibition of an already genetically predisposed decreased functioning UROD. The reduction of free iron and prevention of hepatic uroporphyrin overload prevents the acceleration of phenotypic PCT expression as well as hepatic injury. To this end, there have been three major modalities of treatment. These treatments include venosection with total body iron depletion, low-dose chloroquine therapy, and chelation with desferrioxamine.

Venosection has proven to be the mainstay of therapy for PCT because of its general ease and efficacy. A study by Moran *et al.* [13] looked at patients in the active phase of PCT and demonstrated a significant iron overload. Then, through phlebotomy these patients were brought into biochemical remission with not only a reduction in phenotypic expression but also normalization of transaminases and an as-expected reduction in serum ferritin levels [13]. From this and other studies, the present recommended treatment course with venosection entails the removal of 500 mL of blood two times per week for 2 to 3 months and then as needed, with a goal of maintaining plasma ferritin levels below 25 μg/L, or a hemoglobin level of 12 g/dL, or a transferritin saturation of approximately 15%. This results in resolution of blisters within the first 2 to 3 months, reduction of skin fragility by 6 to 9 months, and normalization of porphyrin concentrations in 13 months [1••,8,11–13,40,42,43•]. It is then through the continued monitoring of urinary porphyrin levels at a recommended 3-month interval that the reactivation of the chronic hepatic porphyria process prior to the development of cutaneous symptoms can be recognized. Venosection is again initiated when urinary porphyrin levels rise above 2 to 4 μmol per 24-hour urine, or are greater than 100 nmol/L.

Chloroquine therapy has been another modality studied as an alternative to the more invasive venosection, or in combination with venosection in more refractory cases. Although its use in higher antimalarial doses has the risk of resulting in a delayed severe hepatotoxic reaction associated with massive uroporphyrinuria with photosensitization and pyrexia, this does not seem to be the case when used in the low doses as it is for PCT treatment. At present, the recommended treatment regiment is 125 to 250 mg twice weekly. The usual effective time frame for blister resolution is 6 months and urinary porphyrin normalization should occur in 6 to 15 months. The proposed mechanism of activity of chloroquine is that it binds to uroporphyrin and promotes its release from hepatocytes by exocytosis. This reduction of intrahepatic uroporphyrin,

and inhibition of uroporphyrin synthesis, results in a reduction of uroporphyrin and its potential complications [11,40,42,43•,44]. The success and relative safety of low-dose chloroquine has been illustrated by multiple studies and case reports. Tsega [44] studied 46 patients who were treated with low-dose chloroquine over a 32-month period and showed no detriment in liver function and eventual resolution of the PCT phenotypic expression. Urinary porphyrin levels less than 100 nmol/L correlated with the resolution of skin manifestations [11,12,42,44]. A significant pitfall of chloroquine management is that when used alone it does not address the core problem of iron overload, which is central to phenotypic expression of PCT. Rather, it is used only to manage the by-product of iron-induced UROD inhibition, uroporphyrin.

A third and less commonly used method described in the literature for the successful treatment of PCT includes chelation with desferrioxamine. This method was proposed and published in *Liver* in 1984 by Gibertini *et al.* [45]. In this study, 16 Italian patients with phenotypic PCT were treated with slow subcutaneous infusion of desferrioxamine 5 nights a week for 8 to 10 hours per night. This was continued until urinary porphyrin excretion normalized. Once this normalization occurred, infusions were reduced to 5 to 10 days per month or every other month depending on urine porphyrin levels needed to maintain phenotypic remission. The attractiveness of this management strategy is that as a chelating agent desferrioxamine removed nonbound iron. This resulted not only in the decrease of total body iron, but more importantly free toxic iron that is implicated in oxidation of uroporphyrinogen into uroporphyrin. Secondly, it was found to have the added benefit of reducing the development of increased intestinal iron absorption that is often seen to accompany phlebotomy-induced anemia. This allowed for a reduction in the compensatory increase in iron absorption that is often seen in the mild anemic state required to maintain remission. No evidence of side effects was seen in this small study group, and the time to control of symptoms was quicker than that needed with venosection. The downside to this treatment, which has prevented its more extensive use, was the relative high cost compared with venosection, the lack of ready and easy-to-use delivery systems, and most importantly a sound indication given the other options, mainly venosection, available for control [45]. Unfortunately, there are little if any data on the treatment of symptomatic PCT specifically in those with HCV.

Impact of HCV on PCT

At present, the literature does not have evidence of large prospective studies comparing the progression of liver injury in patients with PCT both treated and untreated when compared with those patients who express PCT and have a concomitant HCV infection. The number of patients with HCV who have PCT is still relatively small, constituting approximately 1% of all patients with HCV. Despite this, there have been studies such as Tsukazaki *et al.* [39] that have shown an accelerated progression toward hepatic fibrosis and scaring when HCV and phenotypic PCT are found in conjunction [39]. This, coupled with the hypothesis that HCV results in decompartmentalization of iron stores resulting in early phenotypic expression of PCT, as well as the lack of evidence that it directly inhibits UROD activity, has led to the focus of the management of iron stores in those patients afflicted with HCV and PCT prior to HCV treatment [13,42,43•].

Treatment of HCV in Those with PCT

The goal of HCV eradication in the PCT population would ideally result in the sustained loss of detectable HCV RNA, as well as the loss of phenotypic expression of PCT as a sign of regression of an active progressive liver injury. Current treatment of HCV with pegylated interferon combined with ribavirin results in a generalized sustained virologic response (SVR) rate in approximately 50% of those treated [46–48]. In the absence of PCT, hepatic iron overload may impact response to HCV therapy.

Over the past decade, the issue of hepatic iron stores and its relationship to successful treatment of HCV has been looked at but not clearly defined. Prospectively and retrospectively, studies have looked at the effects of elevated serum and hepatic iron levels, as well as the effects of phlebotomy for iron reduction on the effectiveness of HCV treatment with therapy regiments deemed standard of care at that time (Table 3) [49,50,51•,52,53•]. It is unclear from these earlier studies if the lack of SVR is as much a result of hepatic iron concentration (HIC) as it is of short and incomplete treatment of HCV by today's standards, genotypic variation, or other unidentified causes. Three of the studies as described in Table 3 [49,50,51•] look at monotherapy with interferon for the treatment of HCV. These studies showed an appreciable decrease in SVR when treatment was performed with an increased HIC and an improvement in response following phlebotomy. Di Bisceglie *et al.* [52], although not showing an improvement in SVR in previous nonresponders to interferon therapy after phlebotomy, did illustrate a reduction in the necroinflammatory changes noted on liver biopsy when comparing pre-phlebotomy with post-phlebotomy liver biopsies.

A recent retrospective study by Rulyak *et al.* [53•] looking at 112 patients who underwent combination therapy with interferon and ribavirin attempted to address the question whether this would 1) reduce the level of hepatic iron stores after treatment, and 2) establish if pretreatment HICs would impact SVR. The reviewed data collected and analyzed in this study did not show a significant response rate difference for SVR based on patients' pretreatment HICs. Further, treatment with pegylated interferon and

Table 3. Studies regarding iron association to HCV treatment

Study	N	Treatment	Mean pertinent iron profiles	Viral response	Comments
Olynyk *et al.* [49]	58	Alpha interferon monotherapy for 6 mo	HIC (μg/g); SVR 548 ± 85; NR 860 ± 100	SVR 24; NR 34	88% of NR had HIC > 1000 μg/g
Ikura *et al.* [50]	63	Alpha interferon monotherapy for 24 wk	HIC (μmol/g); SVR 24 (1478); TVR 23.9 (8.8–58); NR 27.6 (8.1–100.3)	SVR 20; TVR 24; NR 19	No significant difference seen in HIC. Portal iron deposits correlate with severity of hepatic inflammation activity, fibrosis, and negatively impacted interferon response
Fontana *et al.* [51•]	82	Group A: Interferon monotherapy for 6 mo	Pretreatment: Group A: serum iron 253 ± 55 (ng/mL); % saturation 33.6 ± 2.12	Group A: SVR 3 (7%); TVR 7 (17%)	Interferon response rates were not significant by *P* value. Group B did have improvement in liver histology compared with group A ($P < 0.05$). Post-phlebotomy criteria: 1) hematocrit < 35%; 2) serum ferritin < 10 ng/mL; 3) % saturation < 10 (2/3 needed prior to treatment)
		Group B: Iron reduction before and during interferon therapy for 6 mo	Pretreatment: Group B: serum iron 235 ± 27 (ng/mL); % saturation 34.6 ± 2.3	Group B: SVR 7 (17%); TVR 15 (37%)	
Di Bisceglie *et al.* [52]	96	Group A: Phlebotomy + interferon therapy for 24 wk	Group A: (post phlebotomy) Ferritin 15.1 (ng/mL); % saturation 6.7	SVR 0	All patients in this study had failed interferon therapy in the past. No SVR was seen in either group. Interferon + phlebotomy showed improved liver histology compared with phlebotomy alone
		Group B: Phlebotomy only	Group B: (post phlebotomy) Ferritin 14.6 (ng/mL); % saturation 7.4		
Rulyak *et al.* [53•]	112	Interferon + ribavirin therapy for 48 wk	SVR: HIC 575 (μg/g); serum ferritin 170 (ng/dL); % saturation 38 NR: HIC 463 (μg/g); serum ferritin 244 (ng/dL); % saturation 36	SVR 60; TVR 17; NR 35	Pretreatment HIC is not an independent predictor of response to combination therapy

HCV—hepatitis C virus; HIC—hepatic iron concentration; NR—nonresponder; SVR—sustained virologic response; TVR—transient virologic response.

ribavirin did not result in an appreciable change in HIC after treatment. Based on this data, the authors suggested that iron depletion would not increase the likelihood of SVR in patients treated with combination therapy. There was no evidence that there was an association between HIC and response to HCV therapy. However, the cause for discrepancies between earlier studies and this most recent publication has not yet been well explained and is in need of further evaluation before a conclusive statement can be made. Further studies comparing phlebotomy and iron reduction in patients with elevated iron levels and HICs against a control group, and the results of this on SVR following peginterferon and ribavirin therapy, still need to be performed in a prospective double-blinded manner.

A review of the English literature provides only limited experience with HCV treatment in patients with PCT. Attempts at eradication of HCV prior to treatment of the underlying PCT process have met with limited success. Standard interferon therapy initiated prior to the quiescence of PCT has resulted only in a transient decrease in HCV-RNA levels with and without evidence of changes in urinary porphyrin and phenotypic skin findings. Even during the transient phenotypic resolution and viral response rates, most studies consistently demonstrated that iron stores with isolated HCV treatment had not been reduced. Given the understanding of the importance of iron in patients with PCT, as well as HCV's effects on free hepatic iron levels, it is assumed that iron plays an impor-

tant role in the recurrence of phenotypic PCT and may influence the lack of sustained HCV viral responses in these patients [54–56]. Therefore, it can be hypothesized that successful eradication of HCV would require not only antiviral therapy with current regimens but also a preemptive reduction in intrahepatic iron loads.

The reduction of iron stores in the patients with HCV with phenotypic PCT can be achieved similarly as in the isolated patient with PCT with the simplest modality available, phlebotomy. Although chloroquine is also an effective means of reducing uroporphyrin levels, it does not address the inciting problem of free iron in the hepatocytes, thus having limited use when considering concomitant HCV treatment in PCT. It seems reasonable to suggest that phlebotomy should be a cornerstone in HCV management in patients with PCT. It would allow for the quiescence of PCT and possibly increase the responsiveness of HCV to interferon and ribavirin therapy as it ameliorates hepatic inflammation with a reduction of iron store [43•,57]. However, given the often significant anemia associated with ribavirin, this strategy of pre-HCV therapy phlebotomy is challenging. There are no controlled trials to help determine the optimal timing of when to stop phlebotomy prior to initiating pegylated interferon and ribavirin. It seems reasonable to allow enough time for the hemoglobin to increase above 12 to 14 g/dL to minimize the chance of ribavirin dose reduction, which has been shown to have significant negative impact on SVR [58]. Given the paucity of data using pegylated interferon and ribavirin in patients with HCV and PCT, the natural history and need for continued iron reduction once SVR to HCV has been achieved is not known.

Conclusions

Given the relatively high proportion of patients with PCT plus HCV infection and the demonstrated accelerated rate of liver injury, it would seem intuitive that anyone with phenotypic PCT should be screened for HCV. Similarly, one should suspect PCT in patients with chronic HCV who present with the typical skin lesions described earlier. Once an HCV infection has been established, aggressive phlebotomy in an attempt to reduce free iron as manifested by phenotypic PCT expression should be attempted. This in theory, although not yet proven with large control studies, should be performed prior to initiation of HCV antiviral treatment to optimize chances for SVR and to limit the rapidity with which hepatic injury is incurred. However, one must balance the control of PCT with iron reduction with its potential adverse effects associated with anti-HCV therapy.

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