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# Deferasirox for Porphyria Cutanea Tarda

## A Pilot Study

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**Objective:** To determine the efficacy and safety of deferasirox (an oral iron-chelating agent approved to reduce iron stores in patients with chronic iron overload due to blood transfusions) in a pilot trial for the treatment of patients with porphyria cutanea tarda (PCT), the most common of the porphyrias and often difficult to treat.

**Design:** Prospective, open-label, noncomparative study.

**Setting:** University-affiliated tertiary health care center in Dallas, Texas.

**Patients:** Ten patients with PCT were enrolled in this 6-month study. The diagnosis was established by documenting the presence of elevated porphyrin level in the urine and a history of developing 3 or more blisters per month for at least 3 months prior to enrollment. Patients were treated with 250 mg/d of deferasirox, with an increase to 500 mg/d after 2 months if new blisters continued to develop.

**Main Outcome Measure:** The improvement in number of blisters at the end of the 6-month treatment period was assessed.

**Results:** Of 10 patients, 8 completed the study. Seven had resolution of blistering, 6 had a reduction in urinary porphyrin levels, and 7 had a reduction in ferritin levels. The treatment was well tolerated.

**Conclusions:** In this small pilot study, deferasirox induced improvement in cutaneous findings of PCT in 8 patients who completed 6 months of treatment. Most patients also had a substantial reduction in urinary porphyrin and ferritin levels. Future larger controlled studies are needed to confirm these findings. Deferasirox may be a useful alternative to existing treatment modalities for PCT.

**Trial Registration:** clinicaltrials.gov Identifier: NCT00599326

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**P**ORPHYRIA CUTANEA TARDA (PCT), the most common of the porphyrias, is caused by an abnormality in the control of heme biosynthesis. The specific enzymatic defect is a decrease in uroporphyrinogen decarboxylase activity in either the liver (for patients with acquired, or type I PCT) or all tissues (for patients with familial, or type II PCT). Reduced uroporphyrinogen decarboxylase activity results in an accumulation of the byproducts of heme biosynthesis, particularly porphyrins.<sup>1</sup> Patients have moderate to severe photosensitivity manifesting as vesicles, bullae, erosions, crusts, scars, and milia on sun-exposed sites as well as hypertrichosis on the face. Porphyria cutanea tarda is often induced in susceptible patients by alcohol, hepatitis C virus, and estrogen.<sup>2</sup>

The main clinical end point in the treatment of PCT is the reduction of symptomatic skin lesions. This is accomplished by the use of photoprotective clothing, zinc and titanium dioxide-containing sunscreens, therapeutic phlebotomy, and antimalarial medications (either hydroxychloroquine or chloroquine). The relationship between the development of blisters and iron metabolism is not straightforward. Though some affected patients frequently have disordered iron metabolism, with mild to moderate hepatic iron overload and elevated serum ferritin level and transferrin saturation, recent investigations have demonstrated that a previously underreported percentage of patients with PCT can have normal ferritin and iron levels.<sup>2</sup> Serial phlebotomy has been shown to decrease the development of blisters in patients with iron overload

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and patients with normal iron stores.<sup>3</sup> Despite the efficacy of phlebotomy, patients often find this treatment to be cumbersome and inconvenient owing to frequent clinic visits, and some patients are unable to undergo phlebotomy because of anemia, human immunodeficiency virus infection, or cardiopulmonary disease.

Chronic iron overload is a serious complication of life-saving blood transfusions, often requiring chelation therapy. The standard for iron chelation therapy for many years was deferoxamine mesylate; however, this treatment requires slow subcutaneous or intravenous infusion over 8 to 12 hours, 5 to 7 days per week; therefore, compliance is often poor.<sup>4</sup> Deferasirox is an oral medication approved for the reduction of iron stores by chelation in patients with chronic iron overload due to blood transfusions.<sup>4</sup> This drug, a member of a new class of tridentate iron chelators, the N-substituted bis-hydroxyphenyl-triazoles, has a half life of 8 to 16 hours, allowing for once-daily dosing. Metabolism and elimination is primarily by glucuronidation, followed by hepatobiliary excretion into the feces. Iron overload is frequently seen in patients with  $\beta$ -thalassemia, and these patients were the first large group treated with deferasirox.<sup>4</sup> It has also been used in the treatment of other iron overload states, such as sickle cell disease<sup>5</sup> and myelodysplastic syndromes.<sup>6</sup> The recommended starting dose for iron overload states secondary to chronic transfusion is 20 mg/kg/d, with an increase in dose for unresponsive patients not to exceed 40 mg/kg/d.

Iron chelation therapy has infrequently been used in the treatment of PCT. Slow infusion of subcutaneous desferrioxamine, an iron chelator, has been reported to reduce iron stores in patients with PCT when given 5 days per week for 11 months, but again, this form of treatment is prolonged and cumbersome for patients.<sup>7</sup> The present trial was undertaken to determine if oral deferasirox could be useful in the treatment of PCT.

## METHODS

Patients with PCT were enrolled in an open-label, noncomparative study with deferasirox for 6 months. This study was approved by the local institutional review board, and all patients gave written informed consent. Inclusion criteria included a diagnosis of PCT, presence of elevated porphyrin level in urine with dominance of uroporphyrins and hepatocarbonyl porphyrins, history of developing 3 or more blisters per month for at least 3 months prior to enrollment, and a ferritin level greater than 25 ng/mL (to convert to picomoles per liter, multiply by 2.247). Exclusion criteria included a family history of PCT or similar condition (to decrease the likelihood of recruiting a patient with variegated porphyria [VP] or another hereditary porphyria), elevated serum creatinine level, history of renal dysfunction, or use of any medication that could depress renal function, patients with PCT controlled by phlebotomy alone, and hepatic transaminase enzyme level above 5 times normal. Molecular analysis of the *UROD* gene was not carried out in this study; therefore, it is not possible to completely rule out familial PCT. Many carriers of *UROD* gene mutations remain silent, so it is possible for a patient with PCT to be the only individual in a family manifesting a familial mutation. Thus, the patients recruited for this study would be more appropriately termed *sporadic PCT*.

Patients were treated with 250 mg/d of deferasirox (1 tablet), with an increase to 500 mg/d (2 tablets) after 2 months if new blisters continued to develop. The starting dose of 250 mg/d corresponds to approximately 5 mg/kg/d. The rationale for this dosing scheme was based on the recommended daily dose in the patient with transfusional iron overload of 20 to 40 mg/kg/d. The patient population in the present study was not transfused and had a lower total body iron burden, so a lower dose was considered to be appropriate.

The primary objective was to eliminate blister formation during the course of the study. Secondary objectives included a decrease in ferritin level, reflecting a reduction in total body iron stores, as well as a decrease in urinary porphyrin level. Monthly clinic visits with a physical examination and monitoring of complete blood cell count, serum ferritin and metabolic panel was performed. Deferasirox (250 mg) tablets were dissolved in water, orange juice, or apple juice and taken at least 30 minutes before or after a meal once daily. Patients were instructed to continue their normal work and leisure activities during the course of the study and to make no changes to their photoprotection and photoexposure habits. Also, to diminish the effect of seasonal variation in sun exposure, patients were recruited year round. Because of rare reports of visual and hearing problems with deferasirox, patients received hearing and eye examinations at the baseline visit as well as at the end of the study. In addition, safety data were collected at each study through evaluation of complete blood cell counts, serum chemistry profiles, and patient symptoms.

## RESULTS

Ten patients were enrolled, of which 8 were compliant with therapy and had evaluable data (**Table**). Of the 2 patients dropped from the study, one patient was lost to follow-up after 2 months and another was noncompliant with medication dosing because of concomitant unrelated medical problems and hospitalizations. Of the 8 patients, 6 tested positive for hepatitis C infection, but their disease was not active, as determined by laboratory testing (evaluation of hepatitis C virus polymerase chain reaction results and transaminase measurements), and were allowed to enter the trial. Of the 8 patients enrolled, 7 were male. One patient did not provide a follow-up 24-hour urine specimen; therefore, partial results are presented for this case. Two patients had elevated 24-hour porphyrin levels and normal levels of uroporphyrinogen but had a diagnosis of PCT made based on exclusion of common triggers of pseudoporphyria, older age at onset (fifth decade), absence of acute attacks, physical examination findings, and skin biopsy results. None of the patients were taking estrogen or other hormones, and all reported no alcohol ingestion during the course of the study. All patients had continued blistering and no adverse effects after 2 months of deferasirox therapy at 250 mg/d; therefore, the dose was increased to 500 mg/d for the remainder of the study (ie,  $\leq 10$  mg/kg/d).

The primary end point of the study was met, with all 8 evaluable patients having a reduction in blistering (**Figure**). The mean blister count decreased from 7 to 0, and 7 patients had complete cessation of blister formation with treatment. Of the 8 patients, 6 had a reduction in urinary porphyrin levels, and all had a decrease in serum ferritin levels (**Table**). Total 24-hour urinary

**Table. Results of Deferasirox Therapy**

Patient No./ Sex/Age, y	Blister Count		Total 24-Hour Urinary Porphyrins, $\mu\text{g/dL}^a$		Total 24-Hour Uroporphyrin, $\mu\text{g/dL}^b$		Ferritin, $\text{ng/mL}^c$	
	Baseline	6 mo	Baseline	6 mo	Baseline	6 mo	Baseline	6 mo
1/M/48	3	0	99	NA	4	NA	151	95
2/M/61	5	0	790	80	20	17	320	275
3/M/53	5	0	2836	534	781	94	363	165
4/M/59	5	0	3405	154	3406	91	403	329
5/M/54	10	2	3061	670	1451	298	647	234
6/M/61	8	0	5316	4196	3546	2596	210	241
7/F/51	8	0	1020	1203	475	643	492	141
8/M/47	15	0	4200	1680	1832	970	470	328
Mean (SD)	7	0	2590 (1807)	1217 (1430)	1644 (1387)	672 (915)	382 (159)	226 (86)

Abbreviation: NA, not available.

<sup>a</sup>Reference range, 16 to 60  $\mu\text{g/dL}$ .

<sup>b</sup>Reference range, 3 to 25  $\mu\text{g/dL}$ .

<sup>c</sup>Reference range, 12 to 300  $\text{ng/mL}$  (to convert ferritin to picomoles per liter, multiply by 2.247).



**Figure.** Porphyria cutanea tarda (patient 6). A, Baseline: multiple blisters, erosions, and scars on dorsum of right hand. B, After 4 months of deferiasirox therapy: resolution of almost all lesions on the right hand.

porphyrin levels fell 53%, from a mean (SD) of 2590 (1807)  $\mu\text{g/dL}$  to 1217 (1430)  $\mu\text{g/dL}$  (reference range, 16-60  $\mu\text{g/dL}$ ). Serum ferritin levels decreased by 41%, from a mean (SD) of 382 (159)  $\text{ng/mL}$  to 226 (86)  $\text{ng/mL}$  (reference range, 12-300  $\text{ng/mL}$ ).

The patients tolerated the medication well. No adverse effects were reported or observed except mild abdominal discomfort for 2 days in 1 patient, which re-

solved spontaneously. There were no drug-related abnormalities in laboratory examination findings. Auditory testing as well as ophthalmologic examinations did not reveal any changes in hearing or vision at the end of the study compared with baseline. The patients found the treatment to be convenient and reported excellent compliance, which was confirmed with pill counts. The maximum number of doses missed by any patient during the 6-month duration of the study was 5.

#### COMMENT

In this small pilot study, all patients with PCT who received oral deferiasirox therapy had resolution of their blistering and most had a substantial reduction in urinary porphyrin and ferritin levels. The drug was tolerated well with minimal adverse effects, and compliance was excellent. There were no significant changes in liver and renal function testing results. Gastrointestinal tolerance was good, and there were no new findings during eye and hearing testing at the end of the study compared with baseline. The lower dose of 5 to 10  $\text{mg/kg/d}$  most likely contributed to the lack of significant adverse effects in our study. Patients 1 and 2 were unusual in that they had clinical signs of PCT but did not have a predominance of uroporphyrinogen in their urine. Occasionally, patients with the cutaneous findings of PCT will have low or normal urine porphyrin levels, in which case stool porphyrins should be evaluated, since these will be elevated in VP.<sup>1</sup> Unfortunately this was not done on these patients; therefore, it is not clear if they actually had PCT or VP. These patients did not have a history of acute attacks and developed skin lesions consistent with PCT later in life, making the overall clinical presentation more consistent with PCT; therefore, these patients were included in our study. Furthermore, these patients had improvement in the clinical signs and symptoms of their disease.

The exact pathomechanism explaining the photosensitivity experienced in PCT has yet to be fully characterized. There are a number of possible contributing fac-



tors, including the generation of free radicals from the interaction of UV light in the Soret band (400-410 nm) with the excess porphyrins.<sup>1</sup> Excess iron independently also contributes to the generation of free radicals (including the highly reactive hydroxyl radical) through the Fenton reaction.<sup>8</sup> Although patients with PCT are not total body iron overloaded, iron may play a pathophysiologic role in the disorder. It has been demonstrated in other studies that the relationship among serum ferritin level, liver iron content, and symptomatic lesions of PCT is complex. Furthermore, even in the setting of normal ferritin level and liver iron content, patients with PCT have improvement of their blistering with phlebotomy.<sup>3</sup> This finding suggests that iron depletion is an efficacious treatment for this disease independent of liver iron content. Iron depletion by deferasirox therapy likely mediates the clinical improvement in patients with PCT. This mechanism is directly analogous to phlebotomy, which has been used with great success in this disorder. Ferritin levels are often followed during phlebotomy therapy, but they do not just reflect iron stores because they can also be modulated by inflammation and liver dysfunction. Therefore, they are not always an accurate reflection of activity in patients with PCT. At present, deferasirox is only approved for iron overload states due to blood transfusions and has the following potential adverse effects:

Selected prescribing information for deferasirox<sup>9</sup>:

1. Drug interactions include antacids and drugs metabolized by the cytochrome enzymes CYP3A4, CYP2C8, and CYP1A2
2. Renal impairment, hepatic impairment, hepatic failure, as well as gastrointestinal hemorrhage have been reported with deferasirox
3. Suggested testing frequency:
  - Creatinine and liver function tests at baseline, 2 weeks, then monthly
  - Dose adjustment for renal impairment
  - Urinary protein should be monitored, frequency not given
  - Auditory testing at baseline, then every 12 months
  - Ophthalmologic testing (slit lamp and dilated funduscopy) at baseline, then every 12 months

Limitations of this study include a small sample size and lack of control patients. In addition, patients may have altered ingestion of alcohol or exposure to sunlight during the course of the study without reporting this to the investigators, potentially causing bias. Nevertheless, the significant decrease in skin blisters along with a reduction of urinary porphyrin and serum ferritin levels suggest that deferasirox may be a useful alternative to existing treatment modalities in the treatment of PCT. Future larger controlled studies are needed to confirm these findings.

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**Online-Only Material:** Listen to an author interview about this article, and others, at <http://bit.ly/MT6e0q>.

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