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Prolonged treatment with open-label pirfenidone in Hermansky-Pudlak syndrome pulmonary fibrosis

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ABSTRACT

Purpose: Limited information is available regarding chronic treatment with pirfenidone, an anti-fibrotic drug. Effects of long-term open-label pirfenidone were evaluated in a small cohort with Hermansky-Pudlak syndrome (HPS), a rare autosomal recessive disorder with highly penetrant pulmonary fibrosis.

Results: Three patients with HPS pulmonary fibrosis treated with open-label pirfenidone and twenty-one historical controls randomized to placebo were studied at a single center. Mean duration of treatment with pirfenidone for 3 patients with HPS pulmonary fibrosis was 13.1 years. Annual changes in FVC and DLCO with pirfenidone treatment were 0.46 and − 0.93% predicted, respectively. In comparison, historical controls randomized to receive placebo experienced mean annual changes in FVC and DLCO of − 4.4 and − 2.3% predicted, respectively. High-resolution computed tomography (HRCT) scans revealed improved ground glass opacities with development of minimal interstitial reticulations in 1 patient after 12.8 years of treatment with pirfenidone. Slowly progressive increase in bilateral interstitial fibrosis developed in a different patient, who received pirfenidone for 18.1 years and died at 73 years of age due to HPS pulmonary fibrosis. Another patient treated with pirfenidone for 8.4 years had attenuated ground glass opacification on HRCT scan and improved oxygenation; this patient died due to chronic complications from colitis, and not pulmonary fibrosis. Adverse effects were generally limited to mild gastrointestinal discomfort and transient elevations of alanine aminotransferase in one patient.

Conclusions: Chronic treatment with pirfenidone may provide clinical benefit with few adverse effects for some patients with HPS pulmonary fibrosis. These results suggest that compassionate use of pirfenidone could be considered on a case-by-case basis for patients with HPS pulmonary fibrosis.

1. Introduction

Pulmonary fibrosis develops in patients with Hermansky-Pudlak syndrome (HPS), a rare autosomal recessive disorder characterized by oculocutaneous albinism and a bleeding diathesis due to improper biogenesis of lysosome-related organelles [1, 2]. Ten genetic types of HPS have been reported, and each HPS type is associated with a defect in the Adaptor Protein-3 complex or the Biogenesis of Lysosome-related Organelles Complex (BLOC)-1, BLOC-2, or BLOC-3 [2–11]. Pulmonary fibrosis is an HPS type-specific manifestation. Children and young adults with HPS type 2 (HPS-2), an Adaptor Protein-3 complex disease, and middle-aged adults with HPS-1 or HPS-4, BLOC-3 diseases, are at risk for the development of pulmonary fibrosis [1, 2, 12–16].

The prognosis of patients with HPS pulmonary fibrosis is poor, and approved medical therapy is not available. Patients with end-stage HPS pulmonary fibrosis succumb to progressive ventilatory failure unless they undergo lung transplantation [17, 18]. Pirfenidone, an oral anti-fibrotic drug, was investigated at the National Institutes of Health (NIH) Clinical Center as treatment for HPS pulmonary fibrosis in two clinical trials [19, 20]. The first study was a Phase 2 trial that showed potential

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benefit in slowing the rate of lung function decline in a subgroup of patients with mild or moderate HPS pulmonary fibrosis [19]. An ensuing study focusing on treatment of this subgroup of patients was inconclusive and stopped early due to medical futility [20]. Given the results of these trials, it is equivocal whether or not pirfenidone is beneficial as treatment for HPS pulmonary fibrosis.

Pirfenidone was also studied as treatment for idiopathic pulmonary fibrosis (IPF). One of two multinational clinical trials (ClinicalTrials.gov, NCT00287729 and NCT00287716) met the primary end point of change in percentage of predicted forced vital capacity (FVC) at 72 weeks [21], and a subsequent multinational Phase 3 trial (ClinicalTrials.gov, NCT01366209) conducted for 52 weeks showed that pirfenidone reduced disease progression in patients with IPF and was associated with acceptable side effects and fewer deaths [22]. Pirfenidone was subsequently approved by the United States Food and Drug Administration as treatment for IPF in 2014.

Many patients with pulmonary fibrosis will likely be treated with pirfenidone for extended intervals of time. One extension study investigating chronic treatment with open-label pirfenidone for IPF generally confirmed its safety and efficacy as treatment for IPF after 122 weeks of therapy [23]. In addition, analysis of pooled data showed that pirfenidone was safe and associated with mild adverse events in patients with IPF receiving treatment for a median duration of 1.7 years [24].

Given the promising results of the initial Phase 2 trial at the NIH Clinical Center investigating pirfenidone as treatment for HPS pulmonary fibrosis, enrolled patients were offered open-label pirfenidone at the conclusion of the study. We report the results of serial clinical evaluations for three patients with HPS pulmonary fibrosis who elected to receive open-label pirfenidone for several years. Compared to controls with HPS pulmonary fibrosis who received placebo during clinical trials at the same study center, progression of HPS pulmonary fibrosis was ameliorated in these three patients treated with open-label pirfenidone. Adverse effects were limited to dyspepsia and mild, intermittent elevations of hepatic transaminases.

2. Materials and methods

2.1. Subject selection and inclusion criteria

Patients provided written informed consent to enroll in protocol 97-HG-0085 (ClinicalTrials.gov, NCT00001596; Therapeutic Clinical Trial of Oral Pirfenidone for the Pulmonary Fibrosis of Hermansky-Pudlak Syndrome), which was approved by the Institutional Review Boards of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Heart, Lung and Blood Institute, and National Human Genome Research Institute. HPS was diagnosed by clinical manifestations, platelet electron microscopy demonstrating absent delta granules, and genotyping. Twenty-one patients with HPS and a FVC of 40–75% of predicted were enrolled in an initial Phase 2 trial; 11 patients were randomized to treatment with pirfenidone and 10 patients received placebo [19]. At the conclusion of this Phase 2 trial, three patients elected to receive open-label oral pirfenidone, 801 mg three times daily, provided initially by MARNAC (Dallas, TX), then by InterMune, Inc. (Brisbane, CA), and then by Genentech (San Francisco, CA) under an Investigational New Drug held by the principal investigator (W.A.G.). A subsequent clinical trial investigating pirfenidone as treatment for mild to moderate HPS pulmonary fibrosis enrolled 35 patients, including 12 patients randomized to receive placebo [20]. A historical control group was comprised of 21 placebo-control patients with HPS pulmonary fibrosis who were evaluated at least twice during either clinical trial. All clinical evaluations were performed at the NIH Clinical Center in Bethesda, Maryland.

2.2. Pulmonary function testing and radiographic imaging

Patients were evaluated at the NIH Clinical Center at baseline, every 4 months during the Phase 2 trial, and approximately every 6–12 months while receiving open-label pirfenidone. Lung function was measured at each visit using standard equipment according to American Thoracic Society recommendations as described [25]; measurements of FVC and diffusion capacity (DLCO) are expressed as percentages of predicted values. Conventional and high-resolution computed tomography (HRCT) scans of the chest were performed yearly without intravenous contrast during end-inspiration in the prone position as described [26].

2.3. Statistical analysis

Values are shown as mean ± standard error of the mean. Unpaired Student's *t*-test was used to analyze significance of difference between means for age, baseline FVC % predicted, and baseline DLCO % predicted (GraphPad Prism 5, GraphPad Software, San Diego, CA). Linear regression of lung function data for patients treated with open-label pirfenidone and repeated measures analysis of lung function data for the placebo group were performed (GraphPad Prism 5).

3. Results

3.1. Patient characteristics

Three patients (2 female, 1 male) with HPS-1 pulmonary fibrosis received open-label pirfenidone. Two patients had been randomized to receive placebo, while another patient received pirfenidone during the initial Phase 2 trial. Their mean age was 40.7 ± 9.0 years when they started treatment with pirfenidone (Table 1). All 3 patients were homozygous for the same mutation (c.1472_1487dup16) in *HPS1*, which is a common variant in patients with HPS-1 who originated from the northwest region of Puerto Rico [1]. The patients did not have a history of smoking, and they experienced dyspnea on exertion. One patient had intermittent wheezing due to asthma that responded to inhaled bronchodilators, and a different patient used supplemental oxygen for chronic hypoxemia. Other manifestations of HPS included oculocutaneous albinism in all three patients and chronic colitis in 1 patient; none experienced excessive bleeding.

Baseline blood testing showed normal electrolytes, creatinine, urea

Table 1
Patient characteristics (Baseline data | Final data).

	Patient 1	Patient 2	Patient 3
Age (yrs)	24 | 37	43 | 51	55 | 73
Gender	male	female	female
Oxygen	no | no	yes | no	no | yes
Asthma	yes	no	no
Colitis	no	yes	no
FVC (% predicted)	75 | 72	50 | 70	68 | 40
DLCO (% predicted)	84 | 74	38 | 48	71 | 10*
HRCT scan findings (baseline)	bilateral ground glass opacities	diffuse ground glass opacities; minimal reticulations	minimal ground glass opacities; reticulations
HRCT scan findings (final)	improved ground glass opacities; new minimal reticulations	improved ground glass opacities; stable reticulations	diffuse fibrosis

DLCO = diffusion capacity.
FVC = forced vital capacity.
HRCT = high-resolution computed tomography.
* DLCO measured at 72 years of age.