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Pirfenidone photosensitization in patients with idiopathic pulmonary fibrosis: a case series

Running head: Pirfenidone photosensitization

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The oral antifibrotic agent, pirfenidone (PFD), 5-methyl-1-phenyl-[1H]-pyridine, is used to treat idiopathic pulmonary fibrosis (IPF), a chronic and fatal lung disease. In trials, PFD reduces disease progression and decreases mortality. The most common side events of PFD are skin manifestations (25%), described as a photosensitivity or rash, but they are not well characterised¹. The objective of the present real-life study was to address the question of skin manifestations in patients treated with PFD for IPF.

We performed a single-centre cross-sectional study of 54 patients treated with PFD for IPF (85% men, median age 74 years, median exposure time 11.9 months), in the Department of Pulmonology (Competence Centre for Rare Lung Diseases), at Rennes University Hospital (CHU), France, between April 2014 and January 2017. The study was approved by the CHU Ethics Committee and all patients signed informed consent in accordance with the principles of the Helsinki Declaration.

Of the 54 patients treated with PFD, 13 (22.2%) experienced skin manifestations. All were declared to the Rennes Pharmacovigilance. This database showed that 12 patients had photosensitivity and one urticaria. Eight patients, none of whom had a history of photosensitive diseases, were assessed by a dermatologist (Table 1). The mean duration between starting PFD and a skin manifestation was 5.5 months. They developed burning erythema followed by hyperpigmentation which was sharply limited to sun-exposed areas (bald head, face, neck, upper chest and/or dorsa of forearms and hands), where sunscreen has not been applied one day after UV exposure. These findings were consistent with a moderate phototoxic reaction. Skin biopsies performed in cases 1, 3 and 6, showed epidermal spongiosis with a lichenoid reaction and moderate dermal perivascular lymphocytic infiltration. Apoptotic keratinocytes were observed in case 1. All patients were successfully treated with topical corticosteroid within 8 days. Three patients discontinued PFD due to gastrointestinal disorders and fatigue. No patient relapsed. Other long-term medication was continued.

Photobiological explorations were realized on the back of patients with an ultraviolet (UV)A lamp (Waldmann® 182, Reischett, France) and a solar simulator (Dermolum UM-UW Müller Elektronik®, Moosinning, Germany) emitting polychromatic spectrum (95% UVA/5% UVB). Polychromatic minimal erythema dose (MED) was evaluated 24 hours after exposure for 5 patients tested in normal values. UVA MED was normal (> 20J/cm²) at baseline in all of the 3 cases evaluated. After skin reaction, the reactivity threshold was lower in UVA: an erythema appeared for 20J/cm² 24 hours after exposure in 6 of 6 patients tested. We examined 5 patients using PFD photopatches (contents of Esbriet® 267mg capsule, 30% petrolatum). The irradiated site of 4 patients was positive one and two days after UVA-irradiation (7J/cm²) with 3 having strong crescendo eczematous reaction. The non-irradiated patch showed no reaction.

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Porphyrins in the blood and urine were assayed at PFD introduction and during the skin manifestations in 3 patients: all were normal. The niacin values of 2 of the 3 patients tested were initially low and were not significantly altered after photosensitivity.

To our knowledge, this study represents the largest documented series of PFD photosensitivity because such sporadic case reports have been only published.²⁻⁶ One fifth of our patients were photosensitive, consistent with data from PFD safety analysis¹. Our patients seen by a dermatologist had clinical features of phototoxicity. All were treated with maximum dose of PFD. Photobiochemical studies demonstrated the phototoxicity of PFD⁷, confirmed by clinical reported cases.^{2,3} Our results do not indicate that phototoxicity is linked to the metabolism of porphyrins or niacin. In patients with low niacin serum concentration, we did not assess their diets and found no drug-induced niacin deficiency.

Furthermore, three cases of PFD photoallergic reaction were recently published.^{4,6} Photoallergic dermatitis is characterised by eczematous eruption starting in light-exposed areas and later spreading to covered sites. This clinical presentation was not found in our patients, but histology (lichenoid pattern) and photopatch testing (crescendo eczematous reaction) were in accordance with photoallergic features. Therefore, we believe the mechanism underlying the PFD photosensitivity involves a combination of photoallergic and phototoxic effects.

Our photobiological explorations showed that UVA irradiation influenced PFD photosensitivity, as in most drug-induced photosensitization.⁸ Very few cases with PFD phototesting have been reported.^{3,6} In one case, UVA and UVB MEDs were decreased.³ Lastly, only one patient had UVA PFD patch and was positive⁶, as in most of our cases tested.

The great photosensitivity of PFD requires optimal management including photoprotection and a close collaboration between dermatologists, pulmonologists and general practitioners.

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Table

Table 1. Clinical, biological, and photobiological characteristics of skin manifestations for patients with idiopathic pulmonary fibrosis treated with pirfenidone and seen by a dermatologist.

Table 1. Clinical, biological and photobiological characteristics of skin manifestations for patients with idiopathic pulmonary fibrosis treated with pirfenidone and seen by a dermatologist.

| Case | Age (y) | Sex | Phototype (Fitzpatrick's classification) | Long-term therapy* | Type of skin side event and dermatological examination | Period of use PFD before skin event, in months | PFD dose on onset of photosensitivity (mg/day) | Treatment | Polychromatic MED (Normal > 1 J/cm ²) before/ during PFD treatment | UVA phototest before PFD starting (20 J/cm ²)** | UVA phototest during skin reaction (20 J/cm ²)** | PFD patch test | Niacin dosage before/during PFD treatment (Normal > 38 µmol/L) | Porphyrins dosage in blood and urine before/during PFD treatment |
|------|---------|-----|--|---|--|--|--|--|--|---|--|-------------------|--|--|
| 1 | 74 | M | III | Lansoprazole, irbesartan, rosuvastatin | Phototoxicity (Grade II) on head and dorsa of hands | 4 | 2403 | Topical corticosteroids, photoprotective measures, PFD continued | ND | ND | ND | ND | ND | ND |
| 2 | 68 | M | III | Lansoprazole, prednisone, simvastatin, valsartan, budesonide/formoterol | Phototoxicity (Grade II) on dorsa of hands | 10 | 2403 | Photoprotective measures, PFD continued | Normal: 1.5/1.25 | - | Erythema | NI :- UVA: + | 40/52 | Normal/ Normal |
| 3 | 77 | F | II | Amlodipine, salbutamol, indacaterol/glycopyrronium, alendronic acid, metoclopramide | Phototoxicity (Grade II) on forehead and dorsa of hands | 3 | 2403 | High potent topical corticosteroids, photoprotective measures. Decrease PFD dose (1602mg) due to digestive disorders | ND | - | Erythema | ND | 22/31 | Normal/ Normal |
| 4 | 68 | M | II | Lercanidipine, olmesartan, fenofibrate, lansoprazole | Phototoxicity (Grade II) on head and neck | 11 | 2403 | Photoprotective measures PFD continued | ND/Normal: 1.25 | ND | Erythema | NI :- UVA :- | ND/35 | ND/Normal |
| 5 | 75 | M | II | Ramipril/hydrochlorothiazide, acetylsalicylate, bisoprolol, lansoprazole, rosuvastatin, amlodipine | Phototoxicity (Grade II) on head, neck, scalp, ears, and dorsum of hands | 5 | 2403 | Topical corticosteroids, PFD discontinued | ND/Normal: 1.75 | - | Erythema | NI: - UVA: ++ | 22/51 | Normal/ Normal |
| 6 | 79 | M | II | Acetylsalicylate, hydrocortisone, levothyroxine, testosterone, bisoprolol, atorvastatin, ramipril, lansoprazole | Phototoxicity (Grade II) on head, neck and dorsa of hands | 2 | 2403 | Topical corticosteroids, PFD discontinued | ND/Normal: 1.75 | ND | Erythema | NI :- UVA : ++ | ND / 35 | ND/ Normal |
| 7 | 68 | F | II | Pantoprazole, rosuvastatin, paroxetine, domperidone, lebrizumab | Phototoxicity (Grade II) on neck, upper chest, dorsa of forearms and hands | 7 | 2403 | Topical corticosteroids, photoprotective measures, PFD continued | ND/Normal: 1.75 | ND | Erythema | NI :- UVA : ++ | ND / 42 | ND/Normal |
| 8 | 66 | M | II | None | Phototoxicity (Grade II) on head and dorsa of hands | 2 | 2403 | Topical corticosteroids, PFD discontinued | ND | ND | ND | ND | ND | ND |

y: years. M: male. F: female. Grade II: according to the Common Terminology Criteria Adverse Event (CTCAE). PFD: pirfenidone. MED: minimal erythema dose. ND: not done. NI: non-irradiated PFD patch test. - : negative reaction. + or ++ : positive reaction according International Contact Dermatitis Research Group (ICDRG) system.

* More than six months

** In our laboratory, the normal values for UVA MED were 21-80 J/cm². MED was considered to be pathological after positive reaction in response to 20J/cm², 24 hours after UVA exposure.