Research letter

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

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Dear Editor, The oral antifibrotic agent, pirfenidone (PFD), 5-methyl-l-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 adverse events of PFD are skin manifestations (25%), described as photosensitivity or rash, but they are not well characterized.[1] 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 gave informed signed consent in accordance with the principles of the Helsinki Declaration.

Of the 54 patients treated with PFD, 13 (24%) experienced skin manifestations. All were declared to 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 (details of the clinical, biological and photobiological characteristics of the skin manifestations in these patients are available directly from the authors). The mean duration between starting PFD and a skin manifestation was 5·5 months. They developed burning erythema followed by hyperpigmentation, 1 day after ultraviolet (UV) radiation exposure, 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. 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 treated successfully 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 a UVA lamp (Waldmann® 182, Reischtett, France) and a solar simulator (Dermolum UM-UW Müller Elektronik®, Moosinning, Germany) emitting a polychromatic spectrum (95% UVA / 5% UVB). The polychromatic minimal erythema dose (MED) was evaluated 24 h after exposure for five patients tested at normal values. UVA MED was normal (> 20 J cm^{-2}) at baseline in each of three cases evaluated. After skin reaction, the reactivity threshold was lower in UVA: erythema appeared for 20 J cm^{-2} 24 h after exposure in six of six patients tested. We examined five patients using PFD photopatches (contents of Esbriet® 267 mg capsule, 30% petrolatum). In four patients the irradiated site was positive 1 and 2 days after UVA irradiation (7 J cm^{-2}) with three having strong crescendo eczematous reaction. The nonirradiated patch showed no reaction.

Porphyrins in the blood and urine were assayed at PFD introduction and during the skin manifestations in three patients: all were normal. The niacin values in two of the three 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 only sporadic case reports have been published.[2–6] One-fifth of our patients were photosensitive, consistent with data from PFD safety analysis.[1] Our patients seen by a dermatologist had clinical features of phototoxicity. All were treated with the maximum dose of PFD. Photobiochemical studies demonstrated the phototoxicity of PFD,[7] 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 characterized 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 a UVA PFD patch test and was positive,[6] as in most of our cases tested.

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

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