Doi: 10.32677/IJCR.2016.v02.i01.004 **Case Report**

Pirfenidone Induced Photosensitivity Reaction in a Patient with Idiopathic Pulmonary Fibrosis

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ABSTRACT

Drug-induced photosensitivity refers to the development of cutaneous disease as a result of combined effects of a chemical and light. Photosensitivity reactions may result from systemic medications and topically applied compounds. Pirfenidone is known to cause photosensitivity reactions, rash, pruritus and dry skin at high doses. However, similar adverse reactions with low doses of Pirfenidone have not been reported. We report a case of photosensitivity reaction induced by low- dose Pirfenidone in a patient with idiopathic pulmonary fibrosis (IPF).

Keywords: *Pirfenidone, Photosensitivity, Rash, Idiopathic Pulmonary Fibrosis.*

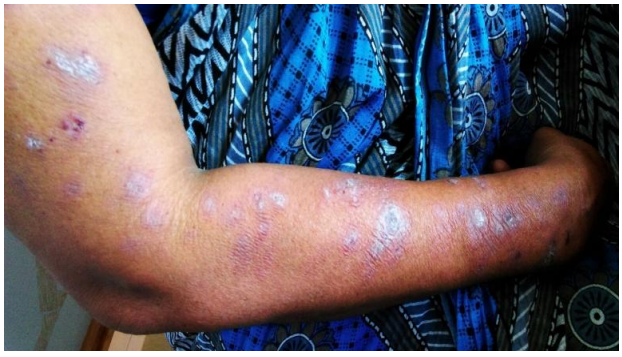
Pirfenidone is an orally administered, synthetic, pyridone compound that is approved in India in 2010 for the treatment of adults with mild to moderate idiopathic pulmonary fibrosis (IPF). The effects of pirfenidone are multitargeted as antioxidant, anti-transforming growth factor (antiTGF) and anti-platelet derived growth factor effects have been demonstrated [1]. It also regulates the activity of TGF-ß and TNF-α [1]. Pirfenidone inhibits cell proliferation, apparently by inhibiting DNA synthesis, in human myometrial and leiomyoma cells and also decreases the levels of mRNAs encoding collagen I and collagen III in these cells [2]. Also, pirfenidone also has been shown to inhibit pulmonary fibroblast expression of heat shock protein 47, a collagen-specific molecular chaperone that is thought to play an important role in extracellular matrix synthesis and remodeling. [3]

The safety profile of pirfenidone is excellent, and it appears to be generally well tolerated. The most common adverse effects include gastrointestinal upset (64%), and fatigue (42%); therefore, drug is to be taken after food, to reduce the nausea and dizziness associated with the drug [4]. A plethora of dermatologic problems including photosensitivity reactions (24%) have also been reported, especially at high doses [4]. However, similar adverse reactions with low doses of Pirfenidone have not been reported. We report a case of rash, scaly plaques and hyper pigmentation of skin induced by low- dose pirfenidone in a female patient diagnosed with IPF.

CASE REPORT

The case involved a 54 year old female diagnosed with IPF in December 2012 and on treatment with pirfenidone 200mg three times a day (600mg/day) orally since February 2013. The diagnosis of IPF was based on history, clinical symptoms and high resolution computed tomography (HRCT) scan findings. She was also on Montelukast 10mg, once daily orally since last 2 months (April 2015) for allergic bronchitis. The patient presented on 13th June 2015 (2 years 4 months after pirfenidone

initiation), with features of rash, scaly papules and hyper pigmentation on right forearm accompanied with severe itching for 5 days. The last dose of pirfenidone was taken on 12th June 2015. The drug was immediately stopped and dermatology consultation was taken. A provisional diagnosis of drug induced photosensitivity reaction with pirfenidone was made on the basis of medical history and clinical examination. The differential diagnosis of actinic lichen planus was also considered.



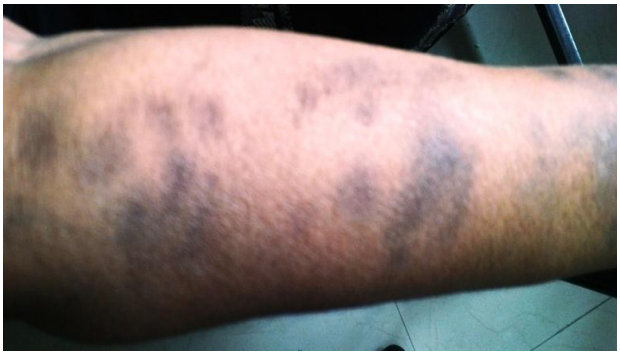


Figure 1 - Skin reaction at the time of presentation. Figure 2 - Skin reaction after one week of Pirfenidone discontinuation

On laboratory investigations, her hemoglobin was low (9.8 g/dl), and absolute eosinophill count (AEC) was raised (440/mm^3). Rest of the tests including leukocyte and platelet counts, hepatic and renal function tests were within normal limits. Biopsy of the skin lesions was planned but the patient refused the biopsy examination. As the patient was on low dose Pirfenidone therapy (600 mg/day), she was completely weaned off the drug and was treated with oral predisolone and antihistamines. She was advised to avoid direct exposure to sunlight, including sun lamps, and to use protective clothing. A sun-screening agent was prescribed. The skin reaction showed significant recovery at the end of one week of pirfenidone discontinuation. This observation enforced the initial diagnosis of pirfenidone induced photosensitivity reaction. Re-challenge after recovery from the reaction was not performed.

DISCUSSION

Skin-related adverse events in the context of pirfenidone therapy can manifest as an erythematous or as a phototoxic burn-like skin rash, occurring on sun-exposed body areas [5]. The underlying mechanism of pirfenidone in photosensitivity reactions is likely to be phototoxic and related to the drug's ability to absorb both ultraviolet (UV) B and UVA [4]. Absorption of UV light by pirfenidone in skin tissue leads to generation of reactive oxygen species and lipid peroxidation resulting in skin lesions [6]. Preclinical animal studies have hypothesized that pirfenidone-induced skin reactions are phototoxic, and therefore proportional to light exposure and drug concentration [7]. Also, it has been demonstrated that the use of a sunscreen with a high protection factor significantly reduces the severity of skin reactions [7].

In the CAPACITY clinical studies with pirfenidone, the most commonly observed skin-related adverse events were photosensitivity reactions and rash. Photosensitivity reaction led to discontinuation in 0.9% pirfenidone-treated patients [8]. In one study which evaluated both high (1800 mg/day) and low-dose (1200 mg/day) pirfenidone compared to placebo, photosensitivity was significantly more common in the pirfenidone-treated subjects regardless of dose [9]. A similar photosensitivity reaction with high dose pirfenidone therapy (600mg/d for 5 months followed by escalation to 1200 mg/d for 10 days) was reported in an elderly man with IPF [10].

Analysis of another clinical trial population showed that skin-related adverse events had a tendency to occur early in the course of treatment and decrease over time [11]. Kaplan-Meier estimates of time to photosensitivity reaction were analyzed in one study. In pirfenidone treatment groups, most patients experiencing photosensitivity or rash did so within the first 24 weeks of treatment. Also in this group, the frequency of photosensitivity reaction or rash was shown to be increased in March, peaked in June, and declined in the autumn. This pattern was not observed in patients treated with placebo. Thus, it was proposed that there may be a significant association of these events to sun exposure in

patients treated with pirfenidone [12]. In our patient, the reaction occurred in the month of June, the dose used was low (600 mg/day), and the duration of treatment was longer (2 years). Hence, pirfenidone induced photosensitivity may not be only dose related and further research should also focus on the duration of therapy.

The standard approach for preventing and managing skin adverse events includes avoiding exposure to direct sunlight (including sunlamps), use of sunscreen active against both UVA and UVB, use of protective clothing, and avoidance of other medicinal products known to cause photosensitivity [12]. Patients experiencing a severe photosensitivity event of sun-exposed skin should be instructed for temporary discontinuation of Pirfenidone, until the skin reaction normalizes. The potential limitation of this case report was that the patient was not re-challenged with pirfenidone after the photosensitivity reaction had subsided.

CONCLUSION

Pirfenidone therapy is generally well tolerated; although, it may require discontinuation of therapy due to skin-related adverse events. In this case, the patient developed photosensitivity reaction with low dose pirfenidone therapy (600 mg/day). Clinicians should monitor the dose and duration of treatment with pirfenidone to prevent occurrence of such reactions.

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