Archivos de Bronconeumología 58 (2022) 710.e1–710.e2

Sociedad Española de Neumología y Cirugía Torácica SEPAR

ARCHIVOS DE Bronconeumología

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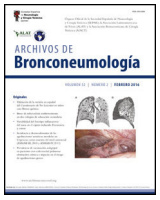

Case report

Desensitization to Pirfenidone in a Patient Diagnosed With Idiopathic Pulmonary Fibrosis and Hypersensitivity to Antifibrotic Drugs

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A 72-year-old man ex-smoker with hypertension and a history of beta-lactam allergy reported dry cough and progressive dyspnea that had first begun 6 months previously. His usual medication included olmesartan 20 mg/d. No environmental exposure or family history of interstitial lung disease was demonstrated. Physical examination revealed baseline oxygen saturation of 96% and bibasilar dry crackles. There were no signs or symptoms of autoimmune disease or involvement of other organs. Serology findings for autoimmunity were completely normal with no other relevant laboratory abnormalities. Spirometry revealed forced expiratory volume in 1 second [FEV_1], 2.37 L [80%]; FVC, 3.35 L [86%]; FEV_1/FVC, 0.70). The diffusing capacity of the lung for carbon monoxide was 80% predicted. High-resolution computed tomography (HRCT) of the chest revealed a subpleural reticular pattern with bibasilar honeycombing indicative of usual interstitial pneumonia (UIP).

The patient was diagnosed with idiopathic pulmonary fibrosis (IPF) and nintedanib 150 mg every 12 h was prescribed. After initiating treatment, he reported facial angioedema, pruritic facial erythema, and edema affecting both hands. Treatment was suspended until further evaluation. At the following visit, he was prescribed pirfenidone and experienced similar symptoms. Given the lack of alternative drugs, the case was discussed with the Allergology Department, and a decision was made to perform a protocol for desensitization to antifibrotic drugs. Skin testing with nintedanib (15 mg/mL and 1.5 mg/mL) and pirfenidone (80 mg/mL and 8 mg/mL) was performed on the patient's forearm in the Allergology Department. Histamine (10 mg/mL) was used as a positive control and sterile saline solution 0.9% as a negative control. Skin prick test was positive for both drugs, with a wheal and flare reaction (4 mm × 4 mm for pirfenidone and 8 × 7 for nintedanib). The same tests were performed as a control on two patients with negative results. We decided to initiate desensitization with pirfenidone since the reaction was smaller. The Pharmacy Department prepared the doses using the 801-mg pirfenidone capsule. Although current evidence for premedication is controversial, we administered cetirizine 10 mg/d and montelukast 10 mg/d before starting desensitization. The first dose was administered in the Allergology Department. Given that the patient only experienced late-onset skin reactions, he continued the protocol at home, with check-ups at the outpatient clinic (Table 1). During the desensitization process, the patient experienced new cutaneous reactions similar to those reported above, thus necessitating de-escalation to doses tolerated during the previous steps and prolongation of the exposure periods. The dose was subsequently increased depending on tolerance. The patient tolerated the full dose of pirfenidone (801 mg tid) after approximately 8 months with functional and radiologic stability of IPF.

Desensitization has proven successful with agents such as antibiotics, chemotherapy drugs, and biologics[1]. However, there are no published protocols for desensitization to pirfenidone or nintedanib. In the present case report, we performed a slow desensitization protocol because the associated skin reactions led us to reduce the dose and prolong exposure. Slow desensitization protocols can prove equally or more effective than rapid protocols according to published articles[2,3].

Finally, the patient was clinically, functionally, and radiologically stable despite having received a low dose of pirfenidone during desensitization. A recent observational study reported that low doses of pirfenidone could prove beneficial for reducing functional progression and for survival in IPF[4]. Song et al.[5] postulated that low doses of pirfenidone (<1200 mg/d) improved gastrointestinal tolerance to the drug with a similar benefit in slowing deterioration of FVC.

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https://doi.org/10.1016/j.arbres.2022.05.005

Table 1
Slow pirfenidone desensitization protocol (target dose, 2403 mg).

Day(s)	Dose in tablets	Dose in mg	Reaction
1	1/16	50.06	No
2	1/16	50.06	No
3	1/16	50.06	No
4	1/8	100.12	No
5	1/8	100.12	No
6	1/8	100.12	No
7	1/4	200.25	No
8	1/4	200.25	No
9	1/4	200.25	No
10	1/2	400.50	No
11	1/2	400.50	No
12	1/2	400.50	No
13	1/2	400.50	No
14	1/2	400.50	No
15	1/2	400.50	**Yes**
16	1/16	50.06	**Yes**
17–31	1/40	20.02	No
32	1/30	26.70	**Yes**
33	1/40	20.02	**Yes**
34	1/30	26.70	**Yes**
35	1/40	20.02	No
36	1/30	26.70	No
37	1/40	20.02	No
38–53	1/40	20.02	No
54–69	1/20	40.05	No
70–85	1/10	80.10	No
86–100	1/10 alternating with 1/5	80.10 alternating with 160.20	No
101–115	1/5 alternating with 1/2	160.20 alternating with 400.50	No
116–130	1/2 alternating with 3/4	400.50 alternating with 600.75	No
131–133	3/4 alternating with 1	600.75 alternating with 801	No
134–136	1	801	No
137–143	1	801	No
144–146	1 alternating with 1 + 1/4	801 alternating with 1001.25	No
147–156	1 + 1/4	1001.25	No
157–159	1 + 1/4 alternating with 1 + 1/2	1001.25 alternating with 1201.5	No
160–179	1 + 1/2	1201.50	No
180–186	1 + 3/4	1401.75	No
187–189	2 alternating with 1 + 3/4	1602 alternating with 1401.75	No
190–199	2	1602	No
200–202	2 alternating with 2 + 1/8	1602 alternating with 1702.12	No
203–205	2 + 1/8 alternating with 2 + 1/4	1702.12 alternating with 1802.25	No
206–212	2 + 1/4	1802.25	No
213–215	2 + 1/4 alternating with 2 + 1/2	1802.25 alternating with 2002.5	No
216–222	2 + 1/2	2002.5	No
223–225	2 + 1/2 alternating with 2 + 3/4	2002.5 alternating with 2202.75	No
226–232	2 + 3/4	2202.75	No
233–235	2 + 3/4 alternating with 3	2202.75 alternating with 2403	No
236–present	3	2403	No

Funding

No funders pertaining to this article.

Conflict of interest

The authors declare not to have any direct or indirect conflict of interest related to the manuscript contents.

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