Trajectory of pulmonary function parameters and radiology progress among patients with Idiopathic pulmonary fibrosis treated with Doxycycline

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ABSTRACT:

Idiopathic pulmonary fibrosis is the most common and lethal form of interstitial lung diseases, with an associated median survival of only 2 to 3 years. Doxycycline through its matrix metalloproteinase inhibition property may be useful in slowing the disease progression among patients with ILD. However, there are only anecdotal reports in the literature in demonstrating long term trajectory in lung function parameters and radiology progress among IPF patients treated with doxycycline. In this report we describe the clinical course of two patients with IPF treated with doxycycline. We also compared the decline in the pulmonary function parameters in our patients with previously published predicted values for normal ageing (non-IPF), placebo, nintedanib and pirfenidone treated patients.

Keywords: Doxycycline, Idiopathic pulmonary fibrosis, Interstitial lung diseases, Pulmonary function test, Nintedanib, Pirfenidone

INTRODUCTION:

Idiopathic pulmonary fibrosis (IPF) is the most common and lethal form of interstitial lung diseases (ILD), with an associated median survival of only 2 to 3 years.[1] The etiology of chronic and progressive IPF is unknown, although potential risk factors such as cigarette smoking and other environmental exposures have been described.[1] While the diagnosis of IPF remains one of exclusion, its definition and the approaches to the management have evolved over the past few decades.[1,2] There has been a shift in the understanding of the pathophysiology of IPF from one of a chronic inflammatory state to one of abnormal wound healing. Aberrant fibroblastic proliferation and accumulation of extracellular matrix (ECM) proteins such as collagen have been the focus of more recent therapeutic interventions for IPF.[3]

In the recent past, anti-fibrotic agents such as Pirfenidone and Nintedanib have been approved for use among patients with IPF and have shown to slow the disease progression.[4,5] However, accessibility and affordability of these newer anti -fibrotic agents can be a hurdle in certain populations, especially in relation to cost in less affluent countries, tolerability and drug related side effects.[6] Nonetheless, there are anecdotal reports in the literature among experimental animal models and in humans to suggest doxycycline through its matrix metalloproteinase inhibition (MMPs) property may be useful in slowing the disease progression among patients with ILD.[7-14] Despite evidence in the literature to suggest doxycycline could be a potential alternate treatment option for patients with ILD/IPF, the trajectory of long term lung function and radiology progression has been sparsely reported among patients treated with doxycycline for ILD/IPF. In this report we describe the clinical course of two patients treated with doxycycline for ILD/IPF.

CASES AND LAB PARAMETERS

Two patients aged 67 (patient A) and 74 (patient B) presented with clinical symptoms and signs along with High-resolution computed tomography (HRCT) findings confirming the diagnosis of ILD/IPF (Figure 1a,b). Both patients had previous smoking history. Patient "A", worked as an occupational health and safety instructor and also previously worked as a marine engineer. He had a background history of coronary artery disease and had undergone coronary artery bypass surgery (CABG). The patients two brothers also had an established diagnosis of IPF. After a period of clinical stability for several years, the patient developed progressive worsening of

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his ILD/IPF related symptoms (Cough and dyspnoea). He voluntarily and as a personal preference opted to be initiated on doxycycline daily as his preferred treatment option. Patient "B", a retired carpenter with a background medical history of hypertension, gastroesophageal reflux disease (GORD), gout and hyperlipidemia presented with symptoms of chronic cough and had a new diagnosis of ILD/IPF. Patient B also declined treatment either with pirfenidone or nintedanib after considering the pros and cons. However, he opted to be treated with doxycycline. Both patients were adherent to therapy and no significant drug related adverse effects were noted secondary to doxycycline, including no significant liver function abnormalities on regular monitoring.

The baseline and trajectory of the pulmonary function test (PFT) results before and after initiating doxycycline are shown in Table 1 a, (patient A,) and Table 1 b (patient B). The initial and follow up PFT flow-volume loops are illustrated chronologically in Figure 2 a (patient A) and Figure 2 b (patient B). Both patients 6 minutes' walk test results are shown in Table 2 a (patient A) and Table 2 b (patient B). The chronological radiological images (Chest X-Ray and chest computed tomography (CT) Scans) are illustrated in Figure 1 a (patient A) and Figure 1 b (patient B).

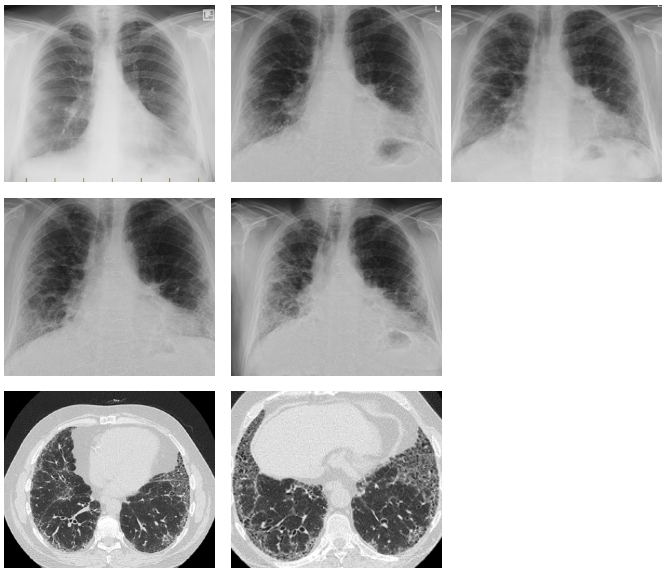


Figure 1 a. Chest X-Ray and chest CT Scans for patient A, showing progressive changes in the interstitial opacity

X-Ray and CT scans arranged chronologically from top left to bottom right (X-Ray: until 74 months) and (CT Chest until 35 months).

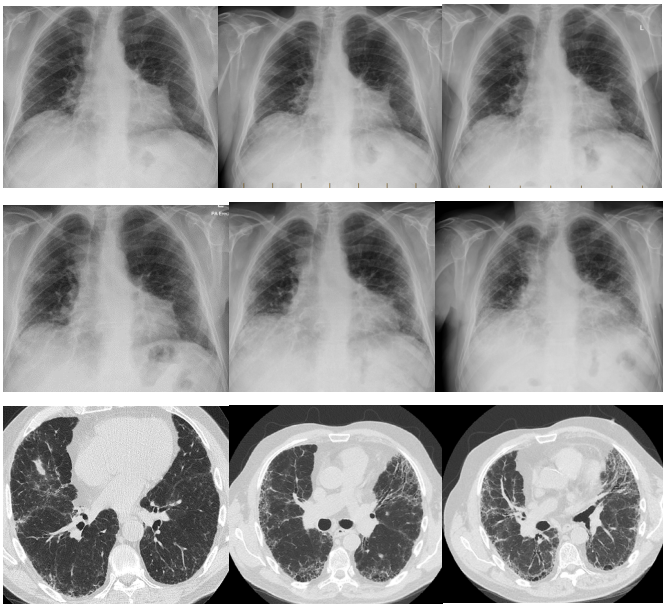


Figure 1 b. Chest X-Ray and CT Scans for patient B, showing progressive changes in the interstitial opacity

X-Ray and CT Scan arranged chronologically from top left to bottom right (X-Ray until 56 months) and (chest CT until 55 months).

Table 1 a. Trajectory of pulmonary function test values from diagnosis of IPF (0 to 74 months) for patient A.

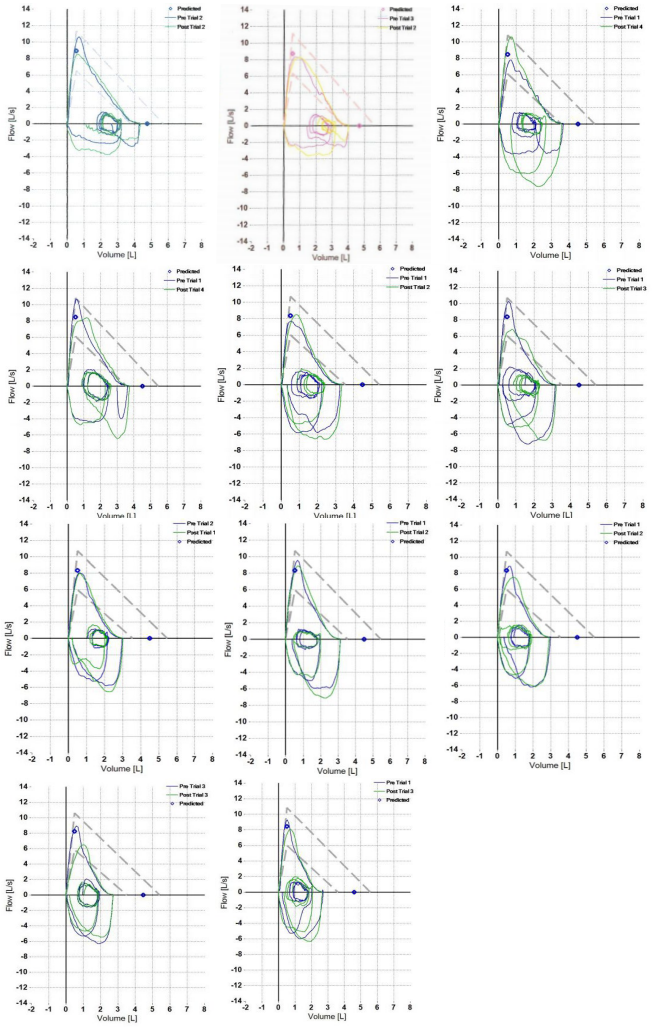
Time (months)	FVC (L)	Predicted FVC	FEV_1 (L)	Predicted FEV_1	FEV_1/FVC	Predicted FEV_1/FVC	DLCO	Predicted DLCO	TLC	Predicted TLC
0	4.3	91%	3.5	100%	0.8	110%	16.5	57%	4.9	67%
21	4.0	86%	3.3	97%	0.8	114%	14.9	52%	4.6	63%
32	3.6	82%	3.0	92%	0.8	112%	13.5	49%	4.2	59%
35	3.6	81%	3.0	91%	0.8	113%	14.9	54%	4.5	62%
#42	3.3	74%	2.7	84%	0.8	114%	12.1	44%	4.1	57%
50	3.2	73%	2.7	83%	0.8	114%	15.8	58%	4.4	61%
52	3.1	71%	2.6	80%	0.8	113%	12.9	47%	0.8	12%
56	2.9	66%	2.4	75%	0.8	114%	11.3	41%	3.9	55%
62	3.1	69%	2.6	80%	0.8	115%	.	.	.	.
66	2.9	66%	2.4	75%	0.8	113%	10.8	39%	3.7	52%
71	2.7	61%	2.3	71%	0.8	116%	11.8	43%	2.3	33%
74	2.7	59%	2.3	69%	0.8	116%	7.1	25%	3.5	47%

Abbreviations: DLCO: Diffusing capacity for carbon monoxide; FVC: Forced vital capacity; FEV_1: Forced expiratory volume in one second; FEV_1/FVC: Forced expiratory volume in one second/ Forced vital capacity ratio; IPF: Idiopathic pulmonary fibrosis; TLC: Total lung capacity. #The shaded cells show when Doxycycline therapy began

Table 1 b. Trajectory of pulmonary function tests values from diagnosis of IPF (0 to 47 months) for patient B.

Time (months)	FVC (L)	Predicted FVC	FEV_1 (L)	Predicted FEV_1	FEV_1/FVC	Predicted FEV_1/FVC	DLCO	Predicted DLCO	TLC	Predicted TLC
0	3.2	86%	2.4	88%	0.7	102%	12.7	53%	4.0	62%
#5	3.0	81%	2.5	92%	0.8	113%	13.4	56%	4.1	62%
6	3.0	83%	2.5	95%	0.8	114%	12.8	54%	3.7	57%
16	3.1	84%	2.5	93%	0.7	109%	10.4	44%	4.6	71%
21	2.9	78%	2.3	86%	0.7	109%	12.1	51%	4.5	69%
31	2.7	75%	2.1	82%	0.7	108%	8.6	37%	3.8	60%
41	2.3	63%	1,7	67%	0.7	105%	8.5	36%	3.3	51%
47	2.2	60%	1,7	63%	0.7	104%	9.5	40%	3.0	45%
62	3.1	69%	2.6	80%	0.8	115%	.	.	.	.
66	2.9	66%	2.4	75%	0.8	113%	10.8	39%	3.7	52%
71	2.7	61%	2.3	71%	0.8	116%	11.8	43%	2.3	33%
74	2.7	59%	2.3	69%	0.8	116%	7.1	25%	3.5	47%

Abbreviations: DLCO: Diffusing capacity for carbon monoxide; FVC: Forced vital capacity; FEV_1: Forced expiratory volume in one second; FEV_1/FVC: Forced expiratory volume in one second/ Forced vital capacity ratio; IPF: Idiopathic pulmonary fibrosis; PFT: TLC: Total lung capacity.
#The shaded cells show when Doxycycline therapy began



February 2018, July 18, December 2018, May 2019, August 2019)

Figure 2 a. Spirometry flow volume loop for patient A. Images arranged chronologically from top left to bottom right. Time since in months - baseline to 74 months.

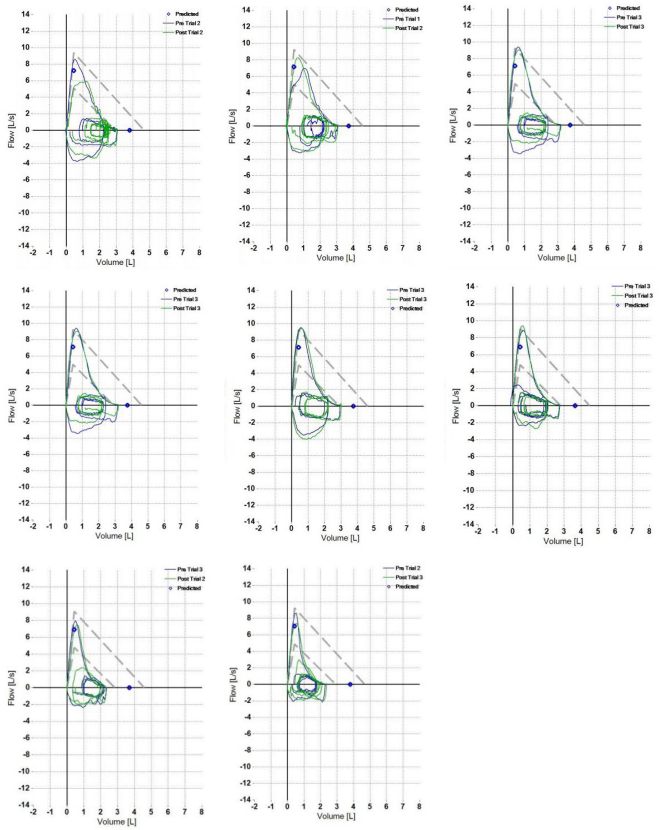


Figure 2 b. Spirometry flow-volume loop for patient B.I mages are arranged chronologically from top left to bottom right Time since in months - baseline to 47 months.

Table 2 a. Six-minute walking test results over time (months) from IPF diagnosis for patient A.

Time (months)	Distance (metres)	HR base (bpm)	Hr Max (bpm)	SpO_2 Base	SpO_2 Min	*Dyspnoea start	*Dyspnoea end	*Fatigue start	*Fatigue end
32	438	79	104	96	91	0	3	0	0
35	516	82	109	95	88	2	3	0.5	0.5
45	468	83	125	96	84	2	4	0	-

*Dyspnoea and Fatigue rated on the Borg scale

Table 2 b. Six-minute walking test results over time (months) from IPF diagnosis for patient B.

Time (months)	Distance (metres)	HR base (bpm)	Hr Max (bpm)	SpO_2 Base	SpO_2 Min	*Dyspnoea start	*Dyspnoea end	*Fatigue start	*Fatigue end
0	578	80	135	95	89	0	0.5	0	0
31	204	83	112	94	89	0	2	0	0
47	384	75	85	94	91	2	10	3	5

*Dyspnoea and Fatigue rated on the Borg scale

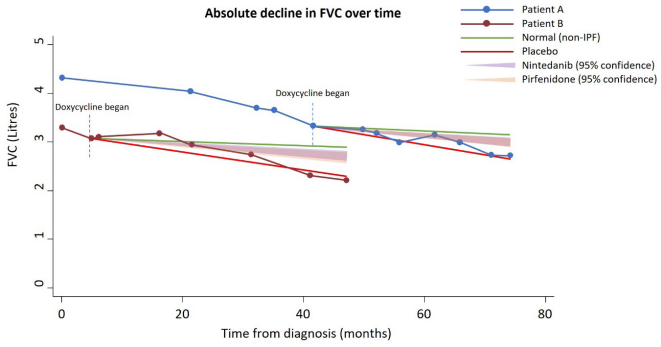


Figure 3. Comparison of the two patients FVC declines with predicted values from the literature for normal ageing (non-IPF), placebo treatment, Nintedanib and Pirfenidone treatment. *Note both nintedanib and pirfenidone overlapped in their effect on FVC.

Abbreviations: FVC: Forced vital capacity; IPF: Idiopathic pulmonary fibrosis

DISCUSSION

A key feature of IPF is the excessive deposition of extracellular matrix and basement membrane disruption that may be at least in part due to an imbalance between secreted matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs)[7,15] that results in a relative overexpression of TIMPs.[16] In spite of their ability to break down the ECM, several MMPs are paradoxically highly upregulated in IPF lungs.[7] One possible explanation for the association between high MMP levels and fibrosis is that MMPs may be mainly expressed outside of the interstitial compartment where collagen is accumulating. Moreover, these proteinases may in fact promote a fibrotic response as a result of their multiple biological functions outside of collagenolysis, including apoptosis, migration, proliferation and angiogenesis.[7] Matrylisin (MMP-7), for example, regulates transforming growth factor beta (TGF-β) activity via the release of pre-formed TGF-β from the extracellular matrix[17], and interaction with osteopontin, an inflammatory cytokine that promotes extracellular matrix deposition and induces growth and migration of fibroblasts and epithelial cells.[18] Inhibition of MMPs therefore represents an attractive therapeutic target in IPF.[19] Doxycyline, an MMP inhibitor, has been observed to attenuate fibrosis, inhibiting MMPs, collagen-1, TGF-β, and Connective tissue growth factor (CTGF) in human type II Alveolar epithelial cells (AECs) and bleomycin-exposed mice.[13]

Both patients presented in this report experienced subjective improvement following initiation of doxycycline. For patient A doxycycline was initiated during the period when the patient demonstrated significant decline in FVC, whereas for patient B doxycycline was initiated at the beginning of the disease spectrum. Comparing the trajectory of progression of FVC between the two patients (Fig 3), although there was progressive decline in FVC, this was to a lesser degree in comparison to the placebo historical cohort, especially during the early stages of treatment. Notably, in the first 18-24 months of treatment for both patients, progression of FVC appeared to match (Patient A) or exceed (Patient B) what would be expected of either Pirfenidone or Nintedanib. After several months of clinical stability, following an episode of lower respiratory tract infection/exacerbation, patient A's condition progressively declined requiring supplemental oxygen therapy and succumbed to his IPF, >2.8 years after initiating doxycycline. For patient B, although the FVC values showed initial improvement after initiating on doxycycline and had been stable for several months on follow up, there has been progressive decline in the FVC values and radiology progression in the later stages of the disease. Patient B is still alive > 4 years after initiating doxycycline. It is unclear if doxycycline would have contributed to longer survival for Patient A if initiated earlier, at the top end of the diseases spectrum as observed in patient B. Comparing our patients PFT parameters with predicted normal decline among patients without IPF and against results of previously published reports among patients on pirfenidone, nintedanib and placebos our results are mixed.[20-23] The initial FVC decline was better in our patients, in particular for patient B, compared to historic placebo control patients with IPF, and similar to previous studies on Nintedanib and pirfenidone.

Doxycycline was tested in two open-label studies among Indian patients, and a non-statistically significant trend toward improved six minutes' walk test (6MWT) and FVC was observed.[10,11] In our patients presented in this report, although there was oxygen desaturation noted on the 6MWT, it was stable during the follow up, at least for patient B. Moreover, for patient B, the walk distance improved as well. A recent larger study that assessed co-trimoxazole or doxycycline to usual care, compared with usual care alone, concluded that antimicrobial therapy did not significantly improve time to nonelective respiratory hospitalization or death.[24] In the above study, although there was no statistically significant difference in the lung function parameters between the co-trimoxazole or doxycycline group and the usual care group, the decline in the lung function values in the treatment arm was observed to be lesser. The authors do acknowledge that a high-powered conclusion cannot be drawn from merely two patients represented in our report and moreover, one cannot compare our patient's outcome to larger aforementioned studies.[24] Furthermore, we did not have control patients to compare. However, we did not observe higher hospitalisation rates in our patients during their disease course. In the absence of extensively published date regarding Doxycycline as a management option for ILD/IPF, small case reports such as this provide additional value to the existing literature and may be of interest to clinicians and researchers. Nonetheless, given the very limited evidence alongside mixed results reported in the literature regarding the utility of doxycycline in the management of ILD/IPF, it is speculative if doxycycline is cleaned up[24] or deserves further research, perhaps in selected phenotypes of ILD/IPF or among patients who may not qualify and in those who are intolerant to other anti-fibrotic therapy.

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