

## Antifibrotics in interstitial lung disease related to connective tissue diseases – a paradigm shift in treatment and outcome

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Dear Editor,

Interstitial lung disease (ILD) is a great challenge in connective tissue diseases (CTD) and an important cause of morbi-mortality.

CTD-ILD pathogenesis includes an initial inflammatory phase<sup>1</sup>, with production of inflammatory mediators responsible for alveolar epithelial damage and recruitment of lung fibroblasts and myofibroblasts<sup>1</sup>. These cells will later produce lung scarring tissue<sup>1</sup> during a subsequent fibrotic phase. Steroids and immunosuppressants remain the first-line treatment for CTD-ILD, but it is urgent to identify new therapies that can change patients' prognosis. Antifibrotics are approved for idiopathic pulmonary fibrosis (IPF) and, due to similar pathogenesis between IPF and CTD-ILD, have been studied in trials in CTD-ILD patients<sup>2,3</sup>.

Herein we report 3 patients with CTD-ILD treated with antifibrotics.

The first patient is a 65-years-old female with positive anti-topoisomerase antibody systemic sclerosis (SSc), diagnosed at the age of 41. She developed ILD with usual interstitial pneumonia (UIP) on high resolution computed tomography (HRCT) 7 years later and was treated with monthly intravenous cyclophosphamide in association with prednisolone (0.5 mg/Kg/day, with subsequent tapering), followed by azathioprine (2mg/kg/day). Due to ILD progression with need for supplementary oxygen, azathioprine was switched for mycophenolate mofetil (MMF; 2g/day). However, fatigue and dyspnoea worsened and, forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLCO) declined. Pulmonary embolism (PE) was excluded and HRCT demonstrated prominent honeycombing without ground glass. We decided to stop MMF and start nintedanib 150mg, twice daily. One

year later she reported subtle clinical improvement, with stable DLCO and slightly increased FVC.

The second patient is a 70-years-old female with positive anti-topoisomerase antibody SSc, diagnosed at the age of 58. Lung involvement was documented since disease presentation, with nonspecific interstitial pneumonia (NSIP) on HRCT. She received monthly intravenous cyclophosphamide for 6 months, and then quarterly for one year, in association with prednisolone (1mg/kg/day, with subsequent tapering), followed by MMF (2g/day). After 15 months on MMF she complained of dyspnoea and fatigue with progressively smaller efforts and need for supplementary oxygen. PE was excluded and FVC and DLCO declined, with concomitant development of new honeycombing and traction bronchiectasis in HRCT, suggesting lung fibrosis progression. MMF was stopped and nintedanib 150mg, twice daily, was started. After six months she reported symptomatic improvement, with functional stability.

The third patient is a 63-years-old female with primary Sjögren's syndrome, positive anti-SSA and anti-SSB antibodies, diagnosed at the age of 49. Asymptomatic lung involvement was documented since disease presentation, with NSIP on HRCT. She was treated with hydroxychloroquine, methotrexate and infliximab for polyarthritis, but two years later, due to refractory arthritis and evidence of progressively active ILD, rituximab was started, with benefit. After 9 cycles of rituximab (1g twice, 2 weeks apart) the patient complained of progressively worsening dyspnoea and fatigue. Complementary exams revealed PE and warfarin was started. Eight months later she became breathless with minimal efforts and HRCT showed new fibrotic linear bands, mainly in lower lobes, with traction bronchiectasis and concomitant ground glass opacities. After excluding cardiac and vascular causes, ILD progression was admitted and pirfenidone 267mg (dose titration to 2403mg/day) was added to rituximab, with symptomatic improvement and functional stability after 6 months.

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**TABLE I. CLINICAL AND FUNCTIONAL OUTCOMES AFTER ANTIFIBROTIC INTRODUCTION**

Patient	CTD	Antifibrotic	Previous immuno-suppression	Concomitant immuno-suppression	Pre-antifibrotic			Post-antifibrotic (6-12 months)		
					Dyspnoea mMRC	FVC (%)	DLCO (%)	Dyspnoea mMRC	FVC (%)	DLCO (%)
1	SSc	Nintedanib	CYC, AZA, MMF	0	4	40.5	15	2/3	53.1	15
2	SSc	Nintedanib	CYC, MMF	0	4	65.9	30	3	65.1	29
3	pSS	Pirfenidone	MTX, IFN	RTX	3/4	46.5	-	2	45.1	-

CTD – connective tissue disease; SSc – systemic sclerosis; pSS – primary Sjögren's syndrome; mMRC – modified medical research council; FVC – forced vital capacity; DLCO – gas transfer; CYC – cyclophosphamide; AZA – azathioprine; MMF – mycophenolate mofetil; MTX – methotrexate; IFN – infliximab; RTX – rituximab

Detailed data on patients' evolution are summarized in Table I.

Nintedanib was preferred due to dosage convenience, except in patient 3 owing to concomitant anticoagulation.

Patients 1 and 3 reported gastrointestinal adverse events, solved with dose reduction and symptomatic medication.

Our work reinforces the promising role of antifibrotics in CTD-ILD, in line with previously published literature<sup>4,5</sup>. Besides, a new treatment strategy, associating antifibrotic with immunosuppressant, is considered for patients with coexistent inflammation and fibrosis. This combining strategy foresees antifibrotics' introduction before established extensive fibrosis, halting disease progression and improving prognosis.

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