LETTERS TO THE EDITOR

Safety data from the use of antifibrotics in connective tissue disease-related interstitial lung disease: particular emphasis on association with immunosuppression

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To the Editor,

Antifibrotic drugs, including nintedanib and pirfenidone, have emerged as an alternative/adjuvant therapy to immunosuppression in connective tissue disease (CTD) – related interstitial lung disease (ILD).

Both drugs are generally well-tolerated. Gastrointestinal complaints, including nausea, vomiting and diarrhea, are the main side effects of nintedanib[1,2], and do not seem to be influenced by the concomitant use of immunosuppression[1]. Besides, as nintedanib inhibits vascular endothelial growth factor and platelet-derived growth factor receptors[3], there is the potential for vascular dysfunction and an increased risk of bleeding. However, real-world data showed a low bleeding incidence in patients treated with nintedanib, irrespective of anticoagulant or antiplatelet therapy received[4]. Regarding pirfenidone, nausea, headache and fatigue are the most reported side effects, and do not seem to be affected by concomitant immunosuppression[5].

In our centre, the first antifibrotic was prescribed in July 2016, and since then 18 patients have been treated with antifibrotics (2 patients have received both nintedanib and pirfenidone). Fifteen of these were under concomitant immunosuppression, which include both conventional and biological disease modifying antirheumatic drugs.

From the 11 patients prescribed with nintedanib, 3 were under stable dose of methotrexate, 3 hydroxychloroquine, 2 leflunomide, 2 mycophenolate mofetil and 4 rituximab. In total, six patients developed gastrointestinal symptoms, mainly nausea and diarrhea. Despite symptomatic treatment, 5 patients had to reduce dose to 100mg bid, with symptoms resolution. The other patient preferred to stop the drug. One patient who switched from pirfenidone to nintedanib due to gastrointestinal complaints also had to reduce dose to 100mg bid because of diarrhea. One patient receiving nintedanib in association with warfarin died of probable alveolar hemorrhage, with an international normalized ratio (INR) > 17. Although it is not possible to attribute a direct causal relationship, since she had a respiratory infection under antibiotics, combining nintedanib and anticoagulant and/or antiplatelet therapy must be done cautiously and weighing the risk-benefit. There were no reports of arterial and/or venous thrombotic events, nor of arterial aneurysms/dissections.

From the 9 patients prescribed with pirfenidone, 1 was under stable dose of methotrexate, 3 leflunomide, 1 azathioprine, 3 rituximab, 1 abatacept, 1 infliximab and 1 tocilizumab. Four patients developed gastrointestinal symptoms, mainly nausea, diarrhea and weight loss. Despite dose reduction to 267mg tid, complaints persisted in 2 patients, who discontinued the drug. One was switched to nintedanib and the other decided to be kept under no treatment. Two patients also developed fatigue and dizziness, which resolved with dose reduction for one patient and led to drug withdrawal in the other. There were no reports of skin rashes or arthralgia.

Table I summarizes demographic data, the underlying CTD and its features, ongoing treatment, adverse events and their management and results from pulmonary function tests at baseline and with at least 9 months of treatment

The experience of our centre reinforces that gastrointestinal (GI) complaints are the most frequent adverse effects related to antifibrotics, regardless of concomitant use of immunosuppression. Antifibrotics did not increase the risk of infection, including respiratory, despite the association with immunosuppression and the presence of permanent lung structural damage. We also did not observe hepatotoxicity with any of the drugs.

Despite scarce data in the literature on the association between immunosuppression and antifibrotics, our experience supports that combining these drugs is safe and targets the two main pathophysiological mechanisms present in CTD-ILD, which include inflammation and fibrosis.

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TABLE I. Summary of demographic data, underlying CTD and its features, ongoing treatment, adverse events and their management and results from pulmonary function tests at baseline and with at least 9 months of treatment§

CTD	Autoantibody profile	Sex/ current age (years)	Antifibrotic	Antifibrotic duration (months)	Concomitant immuno-suppression	Adverse event	Attitude towards adverse event	Outcome	PFTs ate baseline		Last PFTs (at least 9 months of treatment)	
									FVC (% predicted)	DLCO (% predicted)	FVC (% predicted)	DLCO (% predicted)
RA	RF+; ACPA+	M/74	Nintedanib	20	PDN (2.5mg/day) ; MTX (20mg/week)	Nausea, diarrhea	Dose reduction to 100mg bid	Symptom resolution	69.5	68.7	61	81
RA	RF+; ACPA+	F/72	Nintedanib	1	PDN (7.5mg/day); MTX (10mg/week), RTX (2x1g, 2 weeks apart)	Nausea, diarrhea	Patient decided to suspend antifibrotic		70	41.9		
RA	RF+; ACPA+	F/71	Nintedanib	3	PDN (5mg/day); HCQ (400mg/day); MTX (20mg/week), LFN (20mg/day), RTX (2x1g, 2 weeks apart)				61	81		
RA	RF+; ACPA+	M/69	Pirfenidone	24	PDN (2.5mg/day); LFN (20mg/day); ABA (750mg/month)				63.4	47.2	59.8	32
RA	RF+; ACPA+	M/64	Pirfenidone	40	RTX (2x1g, 2 weeks apart)				51.5	30.4	54	22
RA	RF+; ACPA+	F/83	Pirfenidone	1	PDN (7.5mg/day); LFN (10mg/day)	Nausea	Patient decided to suspend antifibrotic		79.2	59.6		
RA	RF+; ACPA+	M/76	Pirfenidone	7	MTX (10mg/week), TCZ (162mg/week)				78	72		
RA	RF+; ACPA+	M/76	Pirfenidone	35	PDN (5mg/day); LFN (20mg/day); IFN (3mg/kg every 8 weeks)				70.1	44	74	57.9
Rhupus	RF+; ACPA+; anti-ds DNA +; anti-Ro60+	F/76	Nintedanib	2	PDN (10mg/day); HCQ (200mg/day), LFN (10mg/day), RTX (2x1g, 2 weeks apart)				78	63		
SSc, limited cutaneous subtype	Anti-Scl70 +	F/75 (†)	Nintedanib	41	MMF (2g/day)				61.5	-	60.6	-
SSc, limited cutaneous subtype	ANA 1/1280; no specificities	F/59	Nintedanib	41	-	Diarrhea (nintedanib)	Dose reduction to 100mg bid	Symptom resolution	80	45	62	-
			Pirfenidone	9		Weight loss and dizziness (pirfenidone)	Dose reduction to 267mg tid	Symptom resolution	62	-	78	50

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TABLE I. continuation

CTD	Autoantibody profile	Sex/ current age (years)	Antifibrotic	Antifibrotic duration (months)	Concomitant immuno-suppression	Adverse event	Attitude towards adverse event	Outcome	PFTs ate baseline		Last PFTs (at least 9 months of treatment)	
									FVC (% predicted)	DLCO (% predicted)	FVC (% predicted)	DLCO (% predicted)
SSc, limited cutaneous subtype	Negative ANA	F/46	Nintedanib	4	-				57.3	41.4		
SSc, limited cutaneous subtype	Negative ANA	F/40	Nintedanib	64	-	Diarrhea	Dose reduction to 100mg bid	Symptom resolution	65	35	57	30
SSc, limited cutaneous subtype	Anti-Scl70 +	F/65 (†)	Nintedanib	13	MMF (2g/day)	Diarrhea Alveolar hemorrhage?	Dose reduction to 100mg bid Death	Symptom resolution	40.5	29.2	52.1	18.1
SSc, diffuse cutaneous subtype	ANA 1/1280; no specificities	F/49	Pirfenidone	10	AZA (2mg/kg/day)	Dizziness	Dose reduction to 801mg bid	Symptom resolution	69	42.4	66	49
pSS	ANA 1/320; anti-SSA+ e anti-SSB+	F/67	Pirfenidone	57	RTX (2x1g, 2 weeks apart)	Nausea, weight loss, fatigue, dizziness	Progressive dose reduction until drug suspension	Symptom resolution	47.3	26.6	56	54
pSS	ANA 1/320; anti-SSA+	F/66	Nintedanib	5	HCQ (400mg/day)				78	63		
DM	ANA 1/160, anti-Ro52+	F/69	Pirfenidone Nintedanib	6 10	MTX (15mg/week); RTX (2x1g, 2 weeks apart)	Nausea, diarrhea (pirfenidone) Diarrhea (nintedanib)	Progressive dose reduction until drug suspension Dose reduction to 100mg bid	Symptom resolution Symptom resolution	61.7	43.6	63	60

*CTD – connective tissue disease; PFTs – pulmonar function tests; FVC – forced vital capacity; DLCO – diffusing capacity for carbon monoxide; RA – rheumatoid arthritis; SSc – systemic sclerosis; pSS – primary Sjögren's syndrome; DM – dermatomyositis ; RF – rheumatoid factor; ACPA - anti-citrullinated protein antibodies; ANA – antinueclear antibodies; F – female; M – male; PDN – prednisolone; MTX – methotrexate; LFN – leflunomide; MMF – mycophenolate de mofetil; AZA – azathioprine; HCQ – hydroxychloroquine; RTX – rituximab; ABA – abatacept; TCZ – tocilizumab; IFN – infliximab

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