Letters to the Editors

Tocilizumab for the treatment of patients with rheumatoid arthritis and interstitial lung diseases: a case series

Sirs,

Rheumatoid arthritis (RA) related interstitial lung disease (ILD) is one of the first causes of death in RA, with a mean survival of 2.6 years after diagnosis (1). The correct therapeutic approach to RA-ILD is still debated, since no controlled studies are available (2). The choice of the treatment is further complicated by the supposed role of many disease-modifying anti-rheumatic drugs (DMARDs) in the onset or worsening of pre-existing ILD (1, 2). Recently, Picchianti Diamanti *et al*., reported a case of a patient with RA-ILD efficaciously treated with tocilizumab (TCZ), speculating about its possible role in this sub-group of patients (2).

In this background, we report our experience of 4 patients with RA-ILD treated with tocilizumab monotherapy, in which remission of RA and stability or improvement of ILD were obtained (see table for clinico-serological data).

Patient 1: treated with methotrexate (MTX) and rituximab (RTX) from 2001 to 2009, when a high resolution computerised tomography (HRCT) showed a thickening of the interstitium of the right lower lobe. Treatment with abatacept was performed until 2013, when, for a low disease control of RA (DAS28 4.77), he underwent intravenous TCZ (560 mg monthly). At that time, HRCT showed a worsening of ILD (reticular lung fibrosis compatible with usual interstitial pneumonia). Joint involvement quickly improved (DAS28 2.64 after 6 months) and after an initial decrease of FVC, the lung function and the extension of reticular lung involvement remained stable along the next 3 years.

Patient 2: treated with sulfasalazine (SFZ) and MTX since 2008. In 2015, ILD was diagnosed, with a non-specific interstitial pneumonia (NSIP) pattern at HRCT. The patient was asymptomatic, FVC was normal, while DLCO was 38%. Because of moderate activity of RA (DAS28 4.87), TCZ was started in 2016, and SFZ and MTX were stopped. After 16 months of therapy, RA was in remission (DAS28 2.53), while lung involvement remained unchanged (no dyspnea, stable HRCT).

Patient 3: overlap syndrome RA-systemic sclerosis, ILD known since 1998, with NSIP pattern at HRCT. She was treated with leflunomide, MTX, SFZ, etanercept and RTX, until 2013, when intravenous TCZ was started for RA high disease activity (DAS28 6.01). Joint involvement rapidly improved. After 30 months, lung involvement was unchanged, but TCZ was stopped for patient's choice.

Patient 4: treated with leflunomide since 2001. In 2008 a combined pulmonary fibrosis and emphysema was diagnosed. In 2016, when the patient underwent our observation, a mild restrictive lung disease was recorded. In January 2017, leflunomide was replaced with TCZ for a low disease control of RA (DAS28 5.44). After 6 months, the patient showed a low disease activity (DAS28 3.03), while no changes were observed in respiratory symptoms and function.

Although the ILD/MTX link is not clearly defined, the use of MTX is nowadays not indicated in patients with RA-ILD (2-4), while it is largely recommended for the management of RA, as first line therapy or in association with biologic DMARDs (5). TCZ could represent a possible safe drug in these patients, considering its efficacy in RA also as monotherapy (6). Moreover, interleukin-6 plays a key role in synovial cell proliferation, but it is also potentially involved in extra-articular manifestations of RA and other connective tissue diseases (7-9).

The management of RA-ILD patients remains a critical unmet medical need. Prospective studies on larger populations are required to define whether biologic or conventional DMARDs could really influence the evolution of ILD in RA patients (2, 10). Moreover, the enrolment of RA patients with an early diagnosis of ILD is mandatory to perform ad hoc studies and clinical trials required to define the best clinical management of a such severe complication in RA patients (11).

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Table I. Clinico-serological features and evolution of the lung function in rheumatoid arthritis patients treated with tocilizumab.

	Sex	Age*	Disease duration (years)	ACPA	RF	Previous treatments	FVC		DLCO		HRCT		Follow-up (months)
							baseline	follow-up	baseline	follow-up	pattern	outcome	
1	M	71	15	+	+	MTX, RTX, ABA	70	63	47	49	UIP	stable	48
2	F	66	9	+	+	SFZ, MTX	94	93	38	44	NSIP	stable	18
3	F	60	12	+	+	LFN, SFZ, MTX, ETN, RTX	106	37	109	37	NSIP	stable	30
4	M	68	21	+	+	LFN	68	69	58	57	CPFE	na	6

*Age at tocilizumab start; ACPA: anticitrullinated peptide antibodies; RF: rheumatoid factor; FVC: forced vital capacity; DLCO: diffusion lung of CO; MTX: methotrexate; SFZ: sulphasalazine; LFN; leflunomide; ETN; etanercept; RTX: rituximab; HRCT: high resolution computed tomography; UIP: usual interstitial pneumonia; NSIP: non-specific interstitial pneumonia; CPFE: combined pulmonary fibrosis and emphysema.