

Effectiveness and safety of tocilizumab for the treatment of refractory systemic sclerosis associated interstitial lung disease: a case series

We read with great interest the results of the double-blind phase 2 faSScinate clinical trial,¹ in which there was encouraging (although not statistically significant) numerical improvement in skin thickening and evidence of less decline in lung function in patients with systemic sclerosis (SSc) treated with tocilizumab (TCZ) compared with those receiving placebo. Initial investigations with TCZ in patients with SSc demonstrated improvements in skin sclerosis and polyarthritides.^{2,3}

Scleroderma-associated interstitial lung disease (SSc-ILD) is a severely debilitating complication with high mortality in extensive disease. There is no approved disease-modifying treatment, and few effective treatment options are available. One of the most urgent needs is to determine which drugs can be useful as a rescue treatment in patients who do not respond to conventional immunosuppressants (cyclophosphamide (CYC) or mycophenolate mofetil (MMF)). In this sense, TCZ appears as one of the most promising candidates and an ongoing 2-year randomised phase 3 trial of TCZ-SC 162 mg in SSc is under way (ClinicalTrials.gov identifier NCT02453256).

Based on this preliminary evidence,¹⁻³ we have evaluated TCZ (off-label use) as a rescue therapy in nine selected patients with progressive SSc-ILD (evidence of clinical and functional decline) despite previous treatment with low-medium prednisone doses, immunosuppressants and rituximab (RTX). They were treated with a compassionate use of TCZ for at least 6 months. In all cases, written informed consent was obtained from the patients,

and the off-label use of TCZ (and previously of RTX) was approved by our local health authorities.⁴

The median durations of SSc and ILD were 8 years (range: 2–15 years) and 7 years (range: 2–12 years), respectively. All cases corresponded to fibrosing non-specific interstitial pneumonia. Progressive interstitial lung disease (ILD) was defined when there was a worsening of $\geq 10\%$ in per cent predicted forced vital capacity (%pFVC) or $\geq 15\%$ in per cent predicted diffusing capacity for carbon monoxide corrected for haemoglobin (%pDLCO) during the follow-up (over 1 year).

Previous or ongoing therapies for SSc-ILD included MMF (100%), CYC (67%), azathioprine (11%) and RTX (100%). In all cases, the time elapsed since the last dose of CYC was greater than 2 years and 6 months in the case of RTX. The mean number of RTX cycles previously administered was 3 ± 1.7 (range: 1–6); in four patients (44%) RTX was discontinued due to adverse events (mainly respiratory or urinary infections and/or transient neutropenia) and in the remaining (56%) due to inefficacy.

TCZ was administered intravenously in two patients (at a dose of 8 mg/kg monthly) and subcutaneously in the remaining 7 (162 mg weekly). In all cases, it was administered with MMF (eight patients received 2 g/day and one patient received 1 g/day). Seven (78%) patients received concomitant treatment with prednisone (≤ 5 mg/day). Ongoing therapy with MMF and oral prednisone remained initially unchanged in all cases.

The baseline clinical features and outcome of these patients are summarised in table 1. At the end of the follow-up period (median 12 months; IQR 25th–75th: 6–33 months), only four patients (44%) were still in treatment. In the other five patients (56%) TCZ was discontinued, due to serious adverse events in one case and due to inefficacy in the other four cases. One of these,

Table 1 Baseline clinical features and outcome of our nine patients with refractory systemic sclerosis-associated interstitial lung disease treated with tocilizumab

Patient number	1	2	3	4	5	6	7	8	9
Age (years)/sex	59/F	40/F	64/F	63/F	57/F	53/F	52/F	60/F	62/F
SSc duration (years)	15	9	12	6	4	6	2	6	10
SSc cutaneous subset	Diffuse	Limited	Diffuse	Limited	Diffuse	Limited	Limited	Diffuse	Diffuse
Chest HRCT pattern of ILD	Fibrosing NSIP	Fibrosing NSIP	Fibrosing NSIP	Fibrosing NSIP	Fibrosing NSIP	Fibrosing NSIP	Fibrosing NSIP	Fibrosing NSIP	Fibrosing NSIP
ILD duration (years)	12	4	12	6	4	6	2	6	9
Autoantibodies	Scl-70 (+) Ro52 (-)	ACA (+) Ro52: ND	Scl-70 (+) Ro52: ND	ACA (+) Ro52 (-)	Scl-70 (+) Ro52 (-)	ACA (+) Ro52: ND	Scl-70 (+) Ro52 (-)	Scl-70 (+) Ro52 (+)	Scl-70 (+) Ro52 (-)
Previous or ongoing therapies for SSc-ILD	CYC IV, MMF, RTX and PDN.	MMF and RTX.	CYC IV, MMF, RTX and PDN.	AZA, CYC IV, MMF, RTX and PDN.	MMF and RTX.	CYC IV, MMF, RTX and PDN.	MMF, RTX and PDN.	CYC IV, MMF, RTX and PDN.	CYC IV, MMF, RTX and PDN.
No of RTX cycles	4	1	4	3	2	5	1	1	6
Follow-up after first dose of TCZ (months)	23	8	34	33	7	6	8	12	18
Lung responses to TCZ therapy*	Pre-TCZ/Post-TCZ %pCVF: 61.7/56.3 (STB). %pTLC: 89.1/62.6. %pDLCO: 30.5/34.6 (STB). 6MWT: 420 m/393 m. HRCT: STB.	Pre-TCZ/Post-TCZ %pCVF: 77.3/80.4 (STB). %pTLC: 88.3/89.1. %pDLCO: 41.4/48.1 (IMPR). 6MWT: 330 m/360 m. HRCT: STB.	Pre-TCZ/Post-TCZ %pCVF: 78.8/73.7 (STB). %pTLC: 75.2/79.8 (STB). %pDLCO: 47.1/50 (STB). 6MWT: 390 m/399 m. HRCT: STB.	Pre-TCZ/Post-TCZ %pCVF: 103/101 (STB). %pTLC: 93/88. %pDLCO: 27/35 (IMPR). 6MWT: 388 m/396 m. HRCT: STB.	Pre-TCZ/Post-TCZ %pCVF: 70.2/60.1 (W). %pTLC: 80.7/66. %pDLCO: 42.1/35.5 (W). 6MWT: 388 m/396 m. HRCT: W.	Pre-TCZ/Post-TCZ %pCVF: 108/112 (STB). %pTLC: ND/ND. %pDLCO: 69/52 (W). 6MWT: ND. HRCT: W.	Pre-TCZ/Post-TCZ %pCVF: 70/56 (W). %pTLC: 83/66. %pDLCO: 61/31 (W). 6MWT: ND. HRCT: W.	Pre-TCZ/Post-TCZ %pCVF: 59/49 (W). %pTLC: 63/57. %pDLCO: 35/30 (W). 6MWT: ND. HRCT: W.	Pre-TCZ/Post-TCZ %pCVF: 80/91 (IMPR). %pTLC: 91/92. %pDLCO: 65/70 (STB). 6MWT: ND. HRCT: ND.
Adverse events	Yes herpeszoster: 1; bacterial infections: 3, needing hospitalisation in one of them (osteomyelitis).	No	No	No	No	No	No	No	No
Discontinuation of the treatment at the endpoint of patient follow-up and reason	Yes, due to adverse events. In waiting list for lung transplantation.	No	No	No	Yes, due to inefficacy.	Yes, due to inefficacy.	Yes, due to inefficacy.	Yes; died due to progression of the ILD	No

HRCT was assessed by one chest radiologist blinded to clinical state or change in lung function. Categorisation of radiological response: (1) improvement (no lung fibrotic changes and improvement $>20\%$ of the extent of ground glass opacities), (2) stabilisation or (3) worsening (if the extent of lung fibrotic changes and/or ground glass opacities increased $>20\%$).

*The evolution of pulmonary function tests was classified according to definitions from the American Thoracic Society into worsening (a decrease of pre-TCZ %pFVC $>10\%$ or %pDLCO $>15\%$), stabilisation (if changes in pre-TCZ %pFVC are less than 10% or 15% in %pDLCO), or improvement (increase of pre-TCZ %pFVC $>10\%$ or %pDLCO $>15\%$).

%pDLCO, per cent predicted diffusing capacity for carbon monoxide corrected for haemoglobin; %pFVC, per cent predicted forced vital capacity; %pTLC, per cent predicted total lung capacity; 6MWT, 6 min walk test; ACA, anticentromere antibodies; AZA, azathioprine; CYC, cyclophosphamide; F, female; HRCT, high-resolution CT; ILD, interstitial lung disease; IMPR, improvement; IV, intravenous; m, metres; MMF, mycophenolate; ND, not done; NSIP, non-specific interstitial pneumonia; PDN, prednisone; RTX, rituximab; Scl70, antitopoisomerase I antibodies; SSc, systemic sclerosis; STB, stabilisation; W, worsening.

four patients died due to progression of ILD. The frequency of adverse events was low, occurring in only one patient (11%) who developed repeat infections including an osteomyelitis complicating a digital ulcer requiring hospitalisation.

Although it is difficult to draw any firm conclusions from these data, according with our experience in this small cohort, TCZ appears to be safe. Its effectiveness as a rescue treatment in patients with refractory SSc-ILD seems modest but not negligible, achieving an improvement or stabilisation of pulmonary function⁵ in 44% of patients.

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