Tocilizumab for systemic sclerosis with cardiac involvement: a case report

Sirs,

Systemic sclerosis (SSc) is characterised by immune dysregulation, microvascular injury, inflammation and fibrosis involving skin and internal organs (1). Clinically evident SSc cardiac involvement occurs in 15–35% of patients with 5-year mortality of 28% (2) in diffuse cutaneous SSc (dcSSc) (2, 3). Treatment of SSc cardiac disease remains challenging, with no disease-modifying targeted therapy (4). Tocilizumab (TCZ), an anti-interleukin-6 (IL-6) receptor antibody, is approved by the U.S. Food and Drug Administration (FDA) for SSc-associated interstitial lung disease (SSc-ILD) (5). Elevated IL-6 contributes to fibrosis and correlates with early disease progression, multi-organ involvement and mortality (6). We report our experience of TCZ in the treatment of two patients with dcSSc, progressive ILD and concomitant cardiac involvement, with resultant improvement summarised in Table I.

Patient 1 was a 51-year-old woman with dcSSc diagnosed in 2013. Cumulative manifestations included Raynaud's phenomenon (RP), skin sclerosis (peak modified Rodnan Skin Score, MRSS 12), gastroesophageal reflux, ILD and cardiac involvement. After 6 monthly doses of intravenous cyclophosphamide and maintenance mycophenolate mofetil (MMF) for skin sclerosis and ILD, disease was well-controlled. In 2016, she developed for the first time arrhythmia (premature ventricular complexes, supraventricular ectopics, atrial flutter) that were not ablated successfully. In 2021, ILD progressed (NYHA I to II, FVC 81-86% to 72% predicted, worsening ground glass opacities/ fibrosis on HRCT), arthritis flared, arrhythmia worsened, and NT-proBNP peaked at 949 pg/ml (normal range <100 pg/ml). Cardiac catheterisation excluded pulmonary hypertension (PH) and coronary artery disease (CAD). Cardiac magnetic resonance imaging (cMRI) confirmed myocardial fibrosis on late gadolinium enhancement (LGE), elevated native T1 values and extracellular volume (ECV). TCZ (12 doses to date) was given with resolution of arthritis and cardiopulmonary improvement (Table I).

Table I. Case reports of tocilizumab for treatment of cardiac involvement in systemic sclerosis

Study	Lee *et al*. (this study); n=2		Campochiaro *et al*. n=1	Ishizaki *et al*. n=1
	Patient 1	Patient 2		
Age/Sex	51/F	45/F	42/M	44/F
Onset of 1st non-RP to cardiac manifestation (year)	6	2	<1	5
Onset of cardiac manifestation to TCZ initiation (year)	5	1	<1	1
Subtype	DcSSc	DcSSc	LcSSc	LcSSc
Autoantibodies	Anti-RNP	Anti-SCL 70	Anti-PM/SCL	Anti-centromere
Cardiac manifestation	Congestive heart failure, tachyarrhythmia	Congestive heart failure	Myocarditis	Tachyarrhythmia
Concomitant manifestation	ILD, GERD, peak MRSS 12	ILD, GERD, digital ulcer, arthritis, peak MRSS 30	ILD, digital ulcer, arthritis	Digital ulcer
Prior treatment	Cyc, MMF	Cyc, MMF, RTX	MMF	MMF
TCZ Regime	IV 8mg/kg monthly	IV 8mg/kg monthly	SC 162mg weekly + MMF	IV8mg/kg monthly
	Pre-TCZ / **Post-TCZ (8 doses)**	**Pre-TCZ** / **Post-TCZ (9 doses)**	**Post-TCZ**	**Post-TCZ**
Biochemical				
Troponin T (ng/L)	<13 / <13	329 / 162	improved	NA
NT-proBNP (pg/ml)	949 / 510	1069 / 391	improved	NA
ESR (mm/hr)	50 / 14	70 / 1	improved	NA
CRP (mg/L)	5,1 / 0,3	15,6 / 0,2	improved	NA
cMRI				
LVEF (%)	45 / 52	31 / 58	Myocardial oedema resolved and LGE slight reduction	Improvement of myocardial BMIPP uptake; LVEF 45% to 59 %
RVEF (%)	48 / 51	24 / 42		
GLS (%)	-13 / -15	NA / NA		
ECV (%)	28 / 25	40 / 39		
Mean native T1 (ms)	1025 / 1019	1207 / 1121		
LGE	No fibrosis / No fibrosis	Patchy RV fibrosis / Patchy RV fibrosis		
Pericardial effusion	Small / Small	Moderate / Small to moderate		
Cardiac catheterisation				
mPAP (mmHg)	22 / NA	18 / NA		
PVR (WU)	1,8 / NA	2,9 / NA		
PCWP (mmHg)	15 / NA	7 / NA		
CI (L/min)	4,0 / NA	4,4 / NA		
pFVC (%)	72 / 77	23 / 44		
pDLCO (%)	54 / 60	NA / 37		

RP: Raynaud's phenomenon; TCZ: tocilizumab; ILD: interstitial lung disease;GERD: gastroesophageal reflux disease; anti-RNP: anti-ribonucleoprotein; MRSS: modified Rodnan skin score; Cyc: cyclophosphamide; MMF: mycophenolate mofotil; RTX: rituximab; SC: subcutaneous; IV: intravenous; NT-proBNP: N-Terminal-proBNP; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; cMRI: cardiac magnetic resonance imaging; BMIPP: myocardiac 123I-bmethyl-p-iodophenyl pentadecanoic acid; LVEF: left ventricle ejection fraction; RVEF: right ventricle ejection fraction; GLS: global longitudinal strain; ECV: extracellular Volume; LGE: late gadolinium enhancement; mPAP: mean pulmonary artery pressure; PVR: pulmonary vascular resistance; PCWP: pulmonary capillary wedge pressure; WU: woods unit; CI: cardiac index; pFVC: predicted forced vital capacity; pDLCO: predicted diffusing capacity of the lung for carbon monoxide; NA: not available.

Patient 2 was a 45-year-old woman with dcSSc diagnosed in 2019. Cumulative manifestations included RP, skin sclerosis (peak MRSS 30), arthritis, myositis, digital ulcers, ILD and cardiac involvement (right ventricular cardiomyopathy with right heart failure). She received intravenous cyclophosphamide (9 doses) and rituximab followed by MMF. MRSS improved to 15, but ILD and cardiomyopathy progressed (NYHA II to IV, recurrent congestive heart failure, FVC 23% predicted, worsening ground glass opacities and fibrosis on HRCT, peak NT-proBNP 1069 pg/ml and troponin-T 329 ng/l). Cardiac catheterisation excluded PH and CAD. cMRI confirmed RV myocardial fibrosis on LGE with elevated T1 values and ECV. TCZ (13 doses to date) was given with cardiopulmonary improvement (Table I).

There is a scarcity of reports that describe TCZ to treat SSc cardiac involvement. In contrast to our patients, two prior cases were of limited cutaneous SSc and received TCZ within 1 year from onset of their cardiac manifestations (7, 8), whereas our patient 1 showed improvement to TCZ 8 years after onset of cardiac manifestation. It is possible that the inflammatory-fibrotic remodelling process is marked by periods of deterioration with recurrent episodes of ischaemia-reperfusion injury and chronic myocardial inflammation that may be amenable to treatment at the time of deterioration.

Troponin and BNP/NT-proBNP are elevated in patients with SSc cardiac involvement and are associated with higher risk of mortality (9-11). Current treatment recommendations for SSc cardiac involvement include MMF, cyclophosphamide and rituximab, which were administered to our patients without response (4). Following TCZ, our patients showed improvement in T1 and ECV values, which detect myocardial interstitial remodelling and fibrosis (12). TCZ blocks IL-6 that drives both inflammatory and fibrotic processes in SSc including cardiomyocyte remodelling (6, 13, 14).

Randomised controlled trials are needed to evaluate the efficacy of TCZ in SSc cardiac involvement. Our report also highlights the potential pivotal role of cMRI T1 mapping in SSc cardiac evaluation to objectively distinguish normal from abnormal myocardium.

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References

1. DI BATTISTA M, BARSOTTI S, ORLANDI M *et al*.:. One year in review 2021: systemic sclerosis. *Clin Exp Rheumatol* 2021; 39 (Suppl. 131): S3-12. https://doi.org/10.55563/clinexprheumatol/izadb8
2. LAMBOVA S: Cardiac manifestations in systemic sclerosis. *World J Cardiol* 2014; 6: 993-1005. https://doi.org/10.4330/wjc.v6.i9.993
3. TYNDALL AJ, BANNERT B, VONK M *et al*.: Causes and risk factors for death in systemic sclerosis: a study from the EULAR Scleroderma Trials and Research (EUSTAR) database. *Ann Rheum Dis* 2010; 69: 1809-15. http://doi.org/10.1136/ard.2009.114264
4. BISSELL LA, ANDERSON M, BURGESS M *et al*.: Consensus best practice pathway of the UK Systemic Sclerosis Study group: management of cardiac disease in systemic sclerosis. *Rheumatology* (Oxford) 2017; 56: 912-21. https://doi.org/10.1093/rheumatology/kew488
5. KHANNA D, LIN C, FURST DE *et al*.: Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med* 2020; 8. https://doi.org/10.1016/S2213-2600(20)30318-0
6. DE LAURETIS A, SESTINI P, PANTELIDIS P *et al*.: Serum interleukin 6 is predictive of early functional decline and mortality in interstitial lung disease associated with systemic sclerosis. *J Rheumatol* 2013; 40: 435-46. https://doi.org/10.3899/jrheum.120725
7. CAMPOCHIARO C, DE LUCA G, TOMELLERI A *et al*.: Tocilizumab for the Treatment of Myocardial Inflammation Shown by Cardiac Magnetic Resonance: Report of Two Cases and Rationale for Its Therapeutic Use. *J Clin Rheumatol* 2021; 27: S476-S9. https://doi.org/10.1097/RHU.0000000000001194
8. ISHIZAKI Y, OOKA S, DOI S *et al*.: Treatment of myocardial fibrosis in systemic sclerosis with tocilizumab. *Rheumatology* (Oxford) 2021; 60(6): e205-e6. https://doi.org/10.1093/rheumatology/keaa865
9. AVOUAC J, MEUNE C, CHENEVIER-GOBEAUX C *et al*.: Cardiac biomarkers in systemic sclerosis: contribution of high-sensitivity cardiac troponin in addition to N-terminal pro-brain natriuretic peptide. *Arthritis Care Res* (Hoboken) 2015; 67: 1022-30. https://doi.org/10.1002/acr.22547
10. ALLANORE Y, KOMOCSI A, VETTORI S *et al*.: N-terminal pro-brain natriuretic peptide is a strong predictor of mortality in systemic sclerosis. *Int J Cardiol* 2016; 223: 385-9. https://doi.org/10.1016/j.ijcard.2016.08.246
11. PAIK JJ, CHOI DY, MUKHERJEE M *et al*.: Troponin elevation independently associates with mortality in systemic sclerosis. *Clin Exp Rheumatol* 2022; 40(10): 1934-41. https://doi.org/10.55563/clinexprheumatol/fytfmy
12. NTUSI NA, PIECHNIK S, FRANCIS JM *et al*.: Subclinical myocardial inflammation and diffuse fibrosis are common in systemic sclerosis--a clinical study using myocardial T1-mapping and extracellular volume quantification. *J Cardiovasc Magn Reson* 2014; 16: 21. https://doi.org/10.1186/1532-429X-16-21
13. MELENDEZ GC, MCLARTY J, LEVICK SP, DU Y, JANICKI JS, BROWER GL: Interleukin 6 mediates myocardial fibrosis, concentric hypertrophy, and diastolic dysfunction in rats. *Hypertension* 2010; 56: 225-31. https://doi.org/10.1161/HYPERTENSIONAHA.109.148635
14. KAWAGUCHI Y: Contribution of Interleukin-6 to the Pathogenesis of Systemic Sclerosis. *J Scleroderma Relat Disord 2017; 2:S6-S12*. 2017; s: S6-S12. https://doi.org/10.5301/jsrd.5000258.