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Anti-interleukin 6 Therapy Effect for Refractory Joint and Skin Involvement in Systemic Sclerosis: A Real-world, Single-center Experience

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ABSTRACT. ***Objective.*** To examine the efficacy and safety of interleukin-6 inhibition by tocilizumab (TCZ) in difficult-to-treat, real-world patients with systemic sclerosis (SSc).

Methods. Twenty-one patients (20 women; 16 diffuse cutaneous SSc; mean age: 52 ± 10 yrs; 10 with early disease [< 5 yrs]; and 11 with long-standing disease [mean disease duration 6.4 ± 3.7 yrs]) with active joint and/or skin involvement refractory to corticosteroids (n = 21), methotrexate (n = 19), cyclophosphamide (n = 10), mycophenolate mofetil (n = 7), rituximab (n = 1), leflunomide (n = 2), hydroxychloroquine (n = 2), and hematopoietic stem cell transplantation (n = 2), who received weekly TCZ (162 mg subcutaneously) in an academic center, were monitored prospectively. Changes in modified Rodnan skin score (mRSS), Disease Activity Score in 28 joints (DAS28), lung function tests (LFTs), and patient-reported outcomes (PROs) were analyzed after 1 year of treatment and at end of follow-up.

Results. One patient discontinued TCZ after 3 months due to inefficacy. During the first year of treatment, improvement was evident in the remaining 20 patients regarding skin involvement (mean mRSS change: −6.9 ± 5.9, $P < 0.001$), polyarthritis (mean DAS28 change: −1.9 ± 0.8, $P < 0.001$), and PROs (all $P < 0.001$); LFT stabilization was observed in 16/20 patients. During the second year, 3 patients discontinued TCZ (cytomegalovirus infection in 1, inefficacy in 2) and 1 died. Beneficial effects were sustained in all 16 patients at end of follow-up (2.2 ± 1.1 yrs), except LFT deterioration in 3 patients. Apart from recurrent digital ulcer infection in 3 patients, TCZ was well tolerated.

Conclusion. TCZ was effective in refractory joint and skin involvement regardless of SSc disease duration or subtype. Long-term retention rates and disease stabilization for most real-world patients suggest that TCZ might be a valuable choice for difficult-to-treat SSc.

Key Indexing Terms: arthritis, disease-modifying antirheumatic drugs, interleukins, systemic sclerosis

Systemic sclerosis (SSc) is a systemic autoimmune disorder characterized by vascular damage and excessive fibrosis of the skin and visceral organs, with several clinical sequelae and in more severe cases, end-stage organ failure. As a result, patients with SSc have a significant impairment of functional status and quality of life as well as high mortality rates.[1] Currently, the mainstay of treatment in SSc comprises vasoactive and immunosuppressive regimens, including methotrexate (MTX), cyclophosphamide (CYC), and mycophenolate mofetil (MMF).[2] However, the low retention rates of these drugs[3] reflect their limitations and the need for new, more potent agents. The pathogenesis of SSc is multifactorial and is characterized by the interplay between a plethora of cell types involving lymphocytes, M2 macrophages, endothelial cells, and fibroblasts.[4] This interplay is mediated by several cytokines with proinflammatory or profibrotic potency,[5] and accumulating evidence during the last 2 decades supports a pivotal role for interleukin (IL)-6.

IL-6 has been detected at high concentrations in the serum and culture supernatants of peripheral blood mononuclear cells[6] of patients with active SSc and is overproduced (as much as 30-fold) from dermal fibroblasts cultured from SSc skin lesions.[7] In vitro studies have shown a profibrotic action of IL-6, such as the IL-6–mediated conversion of fibroblasts to activated myofibroblasts, the induction of overexpression of α-smooth muscle actin protein in dermal fibroblasts, or the endothelial cell activation and apoptosis through IL-6 transsignaling.[8,9] Moreover, bleomycin-induced scleroderma was less severe in transgenic IL-6 knockout mice compared to wild type in which skin sclerosis

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The authors declare no conflicts of interest relevant to this article.

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was also mitigated after blockade of IL-6 activity.[10] Finally, other studies have reported that serum IL-6 levels correlate to disease severity.[11,12]

Based on these experimental and clinical data, IL-6 has been considered a potential therapeutic target.[13] Two observational studies,[14,15] and mainly a phase II and a phase III double-blind, randomized controlled trial (RCT) in patients with SSc,[16,17] have examined the effects of tocilizumab (TCZ), an IL-6 receptor antagonist approved for the treatment of rheumatoid arthritis (RA) and giant cell arteritis.

Our objective was to evaluate the efficacy and safety of TCZ in SSc patients with refractory joint and/or skin involvement in a real-world single-center study.

METHODS

In this prospective study, we included all patients in our academic center fulfilling the 2013 American College of Rheumatology/European League Against Rheumatism classification criteria for SSc[18] who were treated with weekly TCZ (162 mg subcutaneously) due to refractory disease from January 2014 and were prospectively monitored up to December 2020. Refractory disease was defined as nonclinical response (i.e., absence of decrease in modified Rodnan skin score [mRSS] or remission of synovitis) and/or prominent active disease (Revised European Scleroderma Trials and Research group [EUSTAR] Activity Index [RAI] > 2.5)[19] despite treatment with at least 1 immunosuppressive agent (conventional or biologic) for a minimum period of 1 year. Joint involvement was defined as the presence of clinically evident synovitis. According to disease duration at TCZ initiation, patients were categorized as having early (< 5 yrs) or long-standing disease (≥ 5 yrs). At TCZ initiation, no other immunosuppressive agent was added while dosage of previously coadministered glucocorticoids or immunosuppressives remained stable during the study period.

Clinical and laboratory variables that were recorded at baseline and at every follow-up visit during TCZ treatment included the following: RAI[19] (for patient visits before 2017, the RAI was calculated retrospectively); mRSS (a minimal decrease of 4.7 was considered clinically important)[20]; Disease Activity Score in 28 joints (DAS28; both mRSS and DAS28 were evaluated by the same physician); erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP); and lung function tests (LFTs; i.e., forced vital capacity [FVC], and diffusing capacity for carbon monoxide [DLCO] corrected for hemoglobin). A decrease of predicted values > 10% for FVC and/or > 15% for DLCO (according to the cut-offs set in the faSScinate and focuSSced trials)[16,17] at the end of every year of treatment and at the end of follow-up was considered clinically significant. Additionally, physician global visual analog scale (VAS) and patient-reported outcomes (PROs) including Scleroderma Health Assessment Questionnaire (SHAQ) and patient global VAS were recorded. Adverse events manifested during TCZ treatment were recorded for all patients.

Off-label use of TCZ was approved for all patients from the National Organization for Medicines. The study protocol was approved by the ethics committee of Laikon University Hospital (approval number 686/23-06-2011). All patients gave written informed consent at enrollment.

Statistics. Categorical variables (expressed as percentages) and continuous variables (expressed as means ± SD) were compared using chi-square test and *t* test, respectively. Comparison of values before and after TCZ treatment were performed with paired samples *t* test. Spearman rank correlation was used to test for any association between the examined variables. Statistical significance was assumed for *P* values < 0.05. All statistical analyses were performed in SPSS version 25.0 (IBM Corp.).

RESULTS

In total, 21 patients (20 women, 16 diffuse cutaneous SSc [dcSSc], aged 52 ± 10 yrs, disease duration 6.4 ± 3.7 yrs) refractory to corticosteroids (n = 21), MTX (n = 19), CYC (n = 10), MMF (n = 7), rituximab (n = 1), leflunomide (n = 2), hydroxychloroquine (n = 2), and hematopoietic stem cell transplantation (n = 2) were included. Baseline disease characteristics of each patient are shown in Table 1. No patient fulfilled criteria for coexistent RA or any other overlap syndrome and none had positive rheumatoid factor or anticyclic citrullinated antibodies. Ten patients had early disease (6 of them also fulfilled eligibility criteria for the faSScinate and the focuSSced trials),[16,17] whereas 11 patients had long-standing disease. According to the RAI, all patients had active disease, with a mean RAI of 4.9 ± 1.8, mean mRSS of 21.1 ± 9.5, and mean DAS28 of 5.2 ± 0.7, whereas 14 patients had radiologically evident interstitial lung disease (ILD). Comparison of demographics and baseline disease characteristics between patients with early or long-standing disease showed no significant differences.

Efficacy. In total, 20 patients completed 1 year of TCZ treatment, and 1 patient withdrew after 3 months due to rapid disease deterioration (Table 2). After the first year of treatment, 12 of 20 patients achieved low disease activity (LDA) with a 3.0 ± 1.9 decrease ($P < 0.001$) in RAI; 15 had numerical improvement in skin thickening, and 13 patients achieved a minimal clinically important decrease in mRSS (for the entire cohort, median change of mRSS −7 [IQR −10 to −3]), 4 had no change, and 1 patient deteriorated. Notably, individual baseline CRP serum levels correlated to decreases of mRSS (r = 0.583, $P = 0.01$). Moreover, 16 of 18 patients with joint involvement, 13 of 15 with polyarthritis, and 3 with oligoarthritis at baseline experienced clinical improvement; this was also depicted in PROs as SHAQ significantly decreased by a mean of −0.6 ± 0.5, with the majority of patients demonstrating greater improvements in the domains of eating, dressing, and grooming. Regarding LFTs, 4 patients had an FVC decrease > 10% and 16 patients remained stable. DLCO decreased > 15% in 2 patients and remained stable in 18 patients. Significant improvements after the first year of TCZ treatment were evident in RAI, mRSS, DAS28, ESR, CRP, SHAQ, and patient and physician global VAS (Table 3; Supplementary Figures 1 and 2, available with the online version of this article).

During the second year of treatment, 3 of 20 patients discontinued TCZ due to adverse events or inefficacy, and 1 patient died due to cardiac arrest in the context of chronic heart conduction disorders. At the end of follow-up (mean treatment period of 2.2 ± 1.1 yrs), the remaining 16 patients on TCZ (7 with early and 9 with long-standing disease at treatment initiation) had preserved the initial clinical improvements and the improved functional status (as reflected in the improved PROs) compared to baseline (Table 2). Regarding LFTs, 13 patients had stable FVC and 16 stable DLCO, whereas 3 (patients 2, 6, and 18; Table 2) presented a decrease in FVC > 10% compared to baseline. Individual changes in clinical and laboratory variables at last follow-up visit are also depicted in Supplementary Figures 3–6 (available with the online version of this article).

Safety. During TCZ treatment, 1 patient developed severe cytomegalovirus infection manifested with fever and hepatitis but

Table 1. Demographics and baseline disease characteristics of 21 patients with systemic sclerosis treated with tocilizumab.

Patient	Sex/ Age, yrs	Type/Major Organ Involvement	Autoantibodies	Disease Duration, yrs	Prior Immunosuppression (Treatment Duration, months)	RAI	mRSS	ESR/ CRP[a]	TJC/ SJC	DAS28	SHAQ	FVC/ DLCO, % Predicted
1	F/35	dcSSc/PF	RF–, CCP–, ANA+, ENA–	4	CS (28), MTX (24), CYC (12), MMF (12)	2.5	14	18/3.2	2/0	3.4	1.5	75/58
2	F/46	dcSSc/–	RF–, CCP–, ANA–, ENA–	2	CS (16), CYC (4), HSCT, MTX (14)	4.75	15	14/6	8/5	4.7	1.8	98/54
3	F/64	dcSSc/PF	RF–, CCP–, ANA+, Topo+	8	CS (64), RTX (12), CYC (8), HSCT, MMF (22), MTX (26)	7.75	29	32/21	5/2	4.4	1.5	69/48
4	F/61	dcSSc/PF	RF–, CCP–, ANA+, ENA–	3	CS (36), CYC (22)	7.75	24	34/67	9/6	5.6	2.1	64/48
5	F/41	dcSSc/PF, HI	RF–, CCP–, ANA+, Topo+	4	CS (46), MTX (46)	2.5	17	50/9	4/1	4.4	0.9	84/65
6	F/54	dcSSc/PF	RF–, CCP–, ANA+,Topo+	12	CS (120), CYC (10), MMF (28), MTX (78)	7.75	42	51/21	10/6	6.2	2.6	69/64
7	F/56	dcSSc/PF	RF–, CCP–, ANA–, ENA–	11	CS (56), MTX (68)	3.75	15	25/27	5/2	4.9	2.0	99/101
8	F/54	lcSSc/RC	RF–, CCP–, ANA+, ENA–	11	CS (110), HCQ (24), LEF (32), MTX (96)	2.5	10	34/8	6/2	5.1	1.5	85/72
9	F/29	dcSSc/PF	RF–, CCP–, ANA–, ENA–	7	CS (14), MMF (36), HCQ (32), MTX (48)	5.25	24	42/16	9/5	5.8	0.25	80/75
10	F/49	lcSSc/PF	RF–, CCP–, ANA+, Topo+	11	CS (64), MTX (50)	4.75	15	32/10	8/5	5.4	0.8	62/43
11	F/59	dcSSc/–	RF–, CCP–, ANA+, Topo+	4	CS (40), MTX (36)	2.5	14	15/4	4/0	3.4	1.0	109/93
12	F/51	dcSSc/PF, HI	RF–, CCP–, ANA+,Topo+	6	CS (72), MMF (38), MTX (28)	7.75	32	45/16	9/5	5.8	2.6	64/50
13	F/66	dcSSc/–	RF–, CCP–, ANA–, ENA–	1	CS (12), MTX (12)	4	42	26/47	10/6	5.6	2.4	116/72
14	M/39	lcSSc/–	RF–, CCP–, ANA+, Topo+	9	CS (106), MTX (76), MMF (15)	5.25	10	28/6	9/5	5.0	1.4	112/78
15	F/59	dcSSc/PF	RF–, CCP–, ANA+, Topo+	12	CS (120), MTX (52), CYC (6), MMF (20), LEF (18)	2.5	16	75/2.4	10/6	6.2	1.6	79/64
16	F/48	dcSSc/PF, HI	RF–, CCP–, ANA–, ENA–	2	CS (14), CYC (14)	4.75	16	62/14	8/6	5.8	1.3	72/54
17	F/51	lcSSc/–	RF–, CCP–, ANA+, ENA–	4	CS (48), CYC (6), MTX (38)	4.75	13	10/4	9/5	4.7	1.3	68/44
18	F/58	dcSSc/PF	RF–, CCP–, ANA+, Topo+	10	CS (115), CYC (6), MTX (94)	6.25	21	56/15	10/6	6.1	2.6	64/47
19	F/67	lcSSc/–	RF–, CCP–, ANA+, Topo+	2	CS (24), MTX (18)	5.25	18	52/29	8/5	5.7	2.9	118/80
20	F/43	dcSSc/PF	RF–, CCP–, ANA+, Topo+	4	CS (48), MTX (48)	6.25	31	28/11	10/5	5.6	0.5	80/43
21	F/56	dcSSc/PF	RF–, CCP–, ANA+, Topo+	7	CS (80), CYC (6), MTX (68)	4	26	45/6	10/5	5.9	0.6	58/42

[a] ESR (mm/h) and CRP (mg/L). ANA: antinuclear antibody; CCP: cyclic citrullinated peptide; CRP: C-reactive protein; CS: corticosteroid; CYC: cyclophosphamide; DAS28: Disease Activity Score in 28 joints; dcSSc: diffuse cutaneous systemic sclerosis; DLCO: diffusing capacity for carbon monoxide; ENA: extracted nuclear antibodies (including anti-SSA, anti-SSB, anti-Sm, anti-RNP, anti-Jo1, antitopoisomerase); ESR: erythrocyte sedimentation rate; FVC: forced vital capacity; HCQ: hydroxychloroquine; HI: heart involvement; HSCT: autologous hematopoietic stem cell transplantation; lcSSc: limited cutaneous systemic sclerosis; LEF: leflunomide; MMF: mycophenolate mofetil; mRSS: modified Rodnan skin score; MTX: methotrexate; TJC: tender joint count; SJC: swollen joint count; SHAQ: Scleroderma Health Assessment Questionnaire; PF: pulmonary fibrosis; RAI: Revised European Scleroderma Trials and Research group Activity Index; RC: renal crisis; RF: rheumatoid factor; RTX: rituximab; Topo: topoisomerase 1.

with no intestine involvement, leading to permanent treatment discontinuation. Additionally, 3 patients developed recurrent infection of digital ulcers (DUs) resulting in temporary drug discontinuation and 1 hospital admission. Regarding laboratory abnormalities, no patient presented liver function tests > 1.5 times the upper limit of normal, cytopenias, or excessive increase in lipid values. No other adverse events, including gut perforation, were noted.

DISCUSSION

Skin thickening is almost ubiquitously present in SSc and according to a EUSTAR analysis of 7286 patients, synovitis is

Table 2. Individual clinical outcomes at last follow-up visit (mean duration of TCZ treatment: 2.2 ± 1.1 yrs) of 21 patients with systemic sclerosis treated with TCZ.

Patient	TCZ Duration, months	Concomitant treatment, (Dose, mg)	mRSS (Change From Baseline)	FVC/DLCO, % Predicted (Change From Baseline)	TJC/ SJC	ESR/ CRP[a]	DAS28 (Change From Baseline)	SHAQ (Change From Baseline)	Treatment Status	AEs
1	3	PSL (10)	24 (+10)	63 (–12)/48 (–10)	2/0	22/2.5	3.4 (0)	2.1 (+0.6)	D/C (inefficacy)	None
2	13	MTX (12.5) + PSL (5)	8 (–7)	86 (–12)/60 (+6)	1/1	5/0.8	2.6 (–2.1)	0.9 (–0.9)	Ongoing	None
3	13	MTX (15)	18 (–11)	71 (+2)/46 (–2)	2/0	18/1.8	3.3 (–1.1)	0.4 (–1.1)	Ongoing	None
4	14	PSL (7.5)	15 (–9)	61 (–3) /44 (–4)	4/1	25/0.9	4.1 (–1.5)	1.5 (–0.6)	Ongoing	None
5	14	MTX (15) + MP (4)	20 (+3)	87 (+3)/67(+2)	5/1	11/6	3.8 (–0.6)	0.9 (0)	D/C (inefficacy)	None
6	15	PSL (7.5)	26 (–16)	57 (–12)/59 (–5)	4/1	14/1.5	3.8 (–2.4)	1.9 (–0.7)	Ongoing	None
7	16	MTX (15)	9 (–6)	97 (–2) /98 (–3)	2/0	12/1.7	3.1 (–1.8)	1.3 (–0.7)	Ongoing	DU infection
8	16	PSL (7.5)	10 (0)	87 (+2)/70 (–2)	2/0	15/2.1	2.8 (–2.3)	1.0 (–0.5)	Ongoing	None
9	17	MTX (20) + MP (6)	15 (–9)	82 (+2)/72 (–3)	2/0	10/0.3	2.9 (–2.9)	0 (–0.25)	Ongoing	None
10	18	MTX (15) + PSL (7.5)	10 (–5)	65 (+3)/41 (–2)	5/1	6/0.8	3.5 (–1.9)	0.6 (–0.2)	Ongoing	None
11	18	PSL (5)	14 (0)	103 (–6)/88 (–5)	3/0	18/8	3.1 (–0.3)	1.0 (0)	D/C (inefficacy)	None
12	22	MP (4)	28 (–4)	60 (–4)/ 47 (–3)	10/4	29/2.6	5.5 (–0.3)	2.4 (–0.2)	Deceased	None
13	22	MTX (15) + PSL (5)	20 (–22)	109 (–7)/70 (–2)	4/1	10/0.7	3.5 (–2.1)	1.4 (–1.0)	Ongoing	None
14	23	MP (4)	10 (0)	79 (–33)/ 53 (–25)	3/1	8/0.5	3.2 (–1.8)	1.0 (–0.4)	D/C (AE)	CMV infection
15	26	MP (4)	12 (–4)	78 (–1)/62 (–2)	4/1	30/0.9	4.0 (–2.2)	0.9 (–0.7)	Ongoing	None
16	29	PSL (7.5)	2 (–14)	80 (+8)/60 (+6)	2/0	8/0.5	2.5 (–3.3)	0.1 (–1.2)	Ongoing	None
17	33	MTX (12.5)	6 (–7)	68 (0) /46 (+2)	3/1	3/0.4	2.3 (–2.4)	0.4 (–0.9)	Ongoing	None
18	37	PSL (7.5)	21 (0)	52 (–12)/36 (–11)	10/4	7/0.1	4.3 (–1.8)	1.8 (–0.8)	Ongoing	DU infection
19	45	PSL (5)	6 (–12)	125 (+7)/89 (+ 9)	2/0	4/0.7	2.4 (–3.3)	1.4 (–1.5)	Ongoing	None
20	59	MP (4) + MTX (20)	18 (–13)	72 (–8)/46 (+3)	3/0	16/0.6	3.3 (–2.3)	0.1 (–0.4)	Ongoing	None
21	70	PSL (5)	18 (–8)	54 (–4)/44 (+2)	4/1	8/1.4	3.2 (–2.7)	0.1 (–0.5)	Ongoing	DU infection

[a] ESR (mm/h) and CRP (mg/L). AE: adverse event; CMV: cytomegalovirus; CRP: C-reactive protein; D/C: discontinuation; DAS28: Disease Activity Score in 28 joints; DLCO: diffusing capacity for carbon monoxide; DU: digital ulcer; ESR: erythrocyte sedimentation rate; FVC: forced vital capacity; MP: methylprednisolone; mRSS: modified Rodnan skin score; MTX: methotrexate; PSL: prednisolone; SHAQ: Scleroderma Health Assessment Questionnaire; SJC: swollen joint count; TCZ: tocilizumab; TJC: tender joint count.

Table 3. Clinical and laboratory variables and measures at baseline and after 1 year of treatment with TCZ in 20 patients with systemic sclerosis.

	Baseline	Year 1	Change	*P*
RAI	5.1 ± 1.8	2.1 ± 1.7	–3.0 ± 1.9	**< 0.001**
mRSS	21.5 ± 9.5	14.6 ± 6.6	–6.9 ± 5.9	**< 0.001**
Tender joints	7.8 ± 2.4	3.8 ± 2.3	4.0 ± 2.5	**< 0.001**
Swollen joints	4.2 ± 1.2	1.2 ± 1.2	3.0 ± 1.7	**< 0.001**
DAS28	5.3 ± 0.7	3.4 ± 0.6	–1.9 ± 0.8	**< 0.001**
FVC% predicted	82 ± 19.5	79 ± 19.1	–2.9 ± 12	0.39
DLCO% predicted	60.4 ± 16.3	61.1 ± 18.4	0.7 ± 12.3	0.84
ESR, mm/h	35.6 ± 17.2	12.9 ± 11.8	–22.8 ± 19.1	**0.001**
CRP, mg/L	13.2 ± 12.5	1.2 ± 2.1	–12 ± 13.1	**0.006**
SHAQ	1.6 ± 0.8	1.0 ± 0.7	–0.6 ± 0.5	**< 0.001**
PtGA VAS (0–100)	37.8 ± 16.8	60.5 ± 15.4	22.7 ± 20.3	**< 0.001**
PGA VAS (0–100)	33.4 ± 13.2	63.2 ± 13.9	29.8 ± 15.6	**< 0.001**

Values are expressed in mean ± SD. Values in bold are statistically significant. CRP: C-reactive protein; DAS28: Disease Activity Score in 28 joints; DLCO: diffusing lung capacity for carbon monoxide; ESR: erythrocyte sedimentation rate; FVC: forced vital capacity; mRSS: modified Rodnan skin score; PGA: physician global assessment; PtGA: patient global assessment; RAI: Revised European Scleroderma Trials and Research group (EUSTAR) Activity Index; SHAQ: Scleroderma Health Assessment Questionnaire; TCZ: tocilizumab; VAS: visual analog scale.

prevalent in approximately 16% of patients with SSc.[21] Both these clinical manifestations are often refractory to standard immunosuppressives and may lead to severe disability due to contractures and persistent synovitis.

An early EUSTAR observational study about the efficacy of TCZ in SSc[14] reported a significant reduction of DAS28 in 15 patients with refractory polyarthritis after a median follow-up of 5 months. Two RCTs, the phase II faSScinate trial[16] and

the phase III focuSSced trial,[17] examined the effect of TCZ on early dcSSc. In both RCTs, the primary endpoint of significant change in mRSS after 24 and 48 months of treatment with TCZ, respectively, was not achieved compared to placebo. However, significant differences in exploratory and secondary endpoints such as the significantly higher number of patients achieving the minimal clinically important decrease in mRSS in the faSScinate trial[16] and an mRSS improvement > 20% in the focuSSced trial,[17] might support a potential beneficial effect of TCZ on skin thickening in some patients. Moreover, in both RCTs, TCZ treatment resulted in FVC stabilization compared to placebo, as well as radiological stabilization in the focuSSced trial, suggesting an antifibrotic effect of TCZ in radiologically evident ILD.[17]

In the present study, we report the efficacy of TCZ in real-world SSc patients with persistent skin and joint manifestations and prior failure to immunosuppressive regimens. Management of these difficult-to-treat patients in daily practice is challenging due to the paucity of therapeutic alternatives. Data regarding the effect of TCZ in such patients are lacking, as in both RCTs,[16,17] a significant proportion of patients were DMARDs-naïve.

Analysis of our data showed significant clinical improvements after 1 year of TCZ treatment, as synovitis remitted in 80%, mRSS significantly decreased in 65%, and LDA was achieved in 60% of our patients. Importantly, in our cohort no patient fulfilled criteria for overlapping RA or other rheumatic diseases, thus precluding any confounding effect of overlap syndromes in our analysis. Accordingly, these clinical improvements were depicted in the functional status, in which SHAQ and patient global VAS were significantly improved. Moreover, TCZ treatment resulted in stabilization of FVC and DLCO in 80% of our patients, in accordance with the faSScinate and focuSSced trial results.[16,17] Notably, the initial beneficial effect of TCZ on joint/skin and pulmonary involvement was preserved in the majority of patients after a mean treatment duration of more than 2 years, consistent with the results of the focuSSced trial,[17] in which TCZ patients had higher retention rates compared to placebo.

Another interesting finding is that 11 patients in our study had disease duration longer than 5 years, representing real-world patients who would be ineligible for the faSScinate or the focuSSced trials; 9 of these 11 patients had significant and sustained clinical improvement with TCZ. Since in both RCTs[16,17] all participants had early disease, this finding suggests that the efficacy of TCZ in SSc may be independent of disease duration. Additionally, we observed that higher baseline CRP levels were associated with greater improvements in mRSS, consistent with the focuSSced trial results,[17] where TCZ exerted a greater effect in patients with elevated CRP. Increased CRP levels are considered an indirect marker of elevated IL-6. Previous studies have shown that 18% of patients with SSc have continuously elevated CRP throughout the disease course, independently of disease duration, and CRP correlates to more severe phenotype with resistance to treatments and worse prognosis.[22,23] Overall, based on these observations, elevated CRP levels might be regarded as a predictive marker for positive response to TCZ treatment.

Finally, only 4 of 20 patients in our study had deterioration of LFTs after the first year of TCZ treatment. Overall, the paucity of evidence regarding TCZ effect on visceral involvement, except the existing data from the faSScinate and the focuSSced trials, indicating a beneficial effect of TCZ in early SSc-ILD,[16,17,24] limits its use in patients with severe major organ involvement. On the other hand, skin thickening is considered a surrogate marker of disease severity and improvement of skin sclerosis has been correlated with less severe organ involvement and higher survival rates.[25] Additionally, increased IL-6 levels, mirroring an underlying sustained systemic inflammation, have been correlated to visceral involvement and worse prognosis.[11,12] Altogether, these data might suggest that the favorable effect of blocking IL-6 activity with TCZ may be extended to the internal organs, resulting in better disease outcomes.[24] Certainly, more RCTs investigating the efficacy of TCZ in different clinical aspects of SSc are needed in order to establish TCZ as an approved treatment for SSc. Approval of TCZ for the treatment of SSc will facilitate its administration in patients wtih SSc since in most countries, TCZ is currently administered for off-label use only after approval from national committees, due to the high cost and limited clinical experience. Notably, very recently TCZ has been approved by the US Food and Drug Administration for the treatment of SSc-ILD.

Regarding safety, 1 patient developed cytomegalovirus infection leading to permanent TCZ withdrawal, while 3 patients had recurrent infected DUs requiring temporary drug discontinuation. The development of DU infections and subsequent osteomyelitis in a limited number of patients was also reported in faSScinate and focuSSced,[16,17] raising awareness for these potential side effects in patients with advanced digital vasculopathy.

The main strengths of our study are the number of patients, as this is the largest real-life observational study published so far, to our knowledge; the inclusion of different SSc subtypes allowing us to test the efficacy of TCZ in patients with different disease characteristics; and the long-term follow-up. All our patients were White, precluding generalizability of our findings to other ethnic groups; however, our study included a representative SSc population followed in one of the largest tertiary academic centers in Greece. It should be also noted that there was no selection bias, since all SSc patients with refractory disease (as previously defined) who were followed prospectively from January 2014 to December 2020 were administered TCZ.

A main limitation of the present study is the lack of a blinded assessor for mRSS and joint counts, possibly influencing the discrimination of the individual clinical improvements attributed to skin or joint improvement. Moreover, synovitis was diagnosed solely by clinical examination and not by ultrasonography, possibly resulting in overdiagnosis of arthritis in some cases. Additionally, the lack of a control group may have resulted in an overestimation of the clinical effect of TCZ, especially regarding patients with long-standing disease for whom a spontaneous regression due to a self-limiting course of the disease is possible. However, our patients with long-standing disease had persistently high disease activity despite prolonged immunosuppression and improved soon after TCZ administration, supporting the beneficial effect of TCZ in these patients.

Accordingly, data regarding RNA polymerase III antibody status, a predictor of severe skin sclerosis, were unavailable and therefore did not allow us to identify patients more likely to have spontaneous regression of skin thickening. Regarding pulmonary assessment, as serial chest computed tomography was not available for all patients, we could not confirm that the functional stability observed was consistent with radiological stabilization in our patients.

In conclusion, our results showed that TCZ may be a therapeutic alternative with possible efficacy for SSc patients with refractory disease, especially for the management of joint and skin involvement, and may significantly ameliorate their functional status, regardless of disease duration. Clearly, more research is needed to define the subgroups of patients who are most likely to benefit from IL-6 inhibition and also to elucidate such effects in the overall morbidity and mortality of SSc.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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