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

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Running head:

Tocilizumab in Systemic Sclerosis

Abstract

Objective

To examine the efficacy and safety of interleukin-6 inhibition by tocilizumab in difficult-to-treat real-world patients with Systemic Sclerosis (SSc).

Methods

Twenty-one patients [20 women, 16 diffuse SSc, mean age: 52±10 years, 10 with early (<5 years) and 11 with long-standing disease (mean disease duration: 6.4±3.7 years)] with active joint and/or skin involvement refractory to corticosteroids (n=21), methotrexate (n=19), cyclophosphamide (n=10), mycophenolate (n=7), rituximab (n=1), leflunomide (n=2), hydroxychloroquine (n=2), and hematopoietic stem cell transplantation (n=2) who received weekly

tocilizumab (162 mg subcutaneously) in an academic center, were monitored prospectively. Changes in modified Rodnan skin score (mRSS), disease activity score (DAS)28, lung function tests (LFTs) and patient reported outcomes (PROs) were analyzed after one year of treatment and at follow-up end.

Results

One patient discontinued tocilizumab 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 $p<0.001$); LFTs stabilization was observed in 16/20 patients. During the second year, 3 patients discontinued tocilizumab (cytomegalovirus infection in 1, inefficacy in 2) and one died. Beneficial effects were sustained in all 16 patients at follow-up end (2.2±1.1 years), except LFTs deterioration in 3. Apart from recurrent digital ulcer infection in 3 patients, tocilizumab was well-tolerated.

Conclusion

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

Introduction

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, SSc patients have a significant impairment of functional status and quality of life and high mortality rates(1). Currently, the mainstay of treatment in SSc comprises vasoactive and immunosuppressive regimens, including methotrexate, cyclophosphamide and mycophenolate mofetil(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, M_2-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 two decades supports a pivotal role also for Interleukin-6 (IL-6).

Interleukin-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 a-smooth muscle actin protein in dermal fibroblasts or the endothelial cell activation and apoptosis through IL-6 trans-signaling(8,9). Moreover, bleomycin-induced scleroderma was less severe in

transgenic IL-6 knockout mice compared to wild type in which skin sclerosis 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)(16,17), have examined the effects of tocilizumab, an IL-6 receptor antagonist approved for the treatment of rheumatoid arthritis and giant cell arteritis, in SSc patients.

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

Materials and Methods

In this prospective study, we included all patients in our academic center, fulfilling the 2013 ACR/EULAR classification criteria for SSc(18), who were treated with weekly tocilizumab (162mg subcutaneously) due to refractory disease from January 2014 and were prospectively monitored up to December 2020. Refractory disease was defined as non-clinical response [(i.e absence of decrease in modified Rodnan Skin Score (mRSS) or remission of synovitis] and/or prominent active disease [(EUSTAR modified activity index (MAI) >2.5] despite treatment with at least one 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

tocilizumab initiation, patients were categorized as early (<5 years) or long-standing disease (>5 years). At tocilizumab initiation, no other immunosuppressive agent was added while dosage of previously co-administered glucocorticoids or immunosuppressives (**Table 2**) remained stable during the study period.

Clinical and laboratory variables that were recorded at baseline and at every follow-up visit during tocilizumab treatment included: EUSTAR MAI(19) (for patients' visits before 2017 the EUSTAR MAI was calculated retrospectively); mRSS (a minimal decrease of 4.7 was considered clinically important)(20); Disease Activity Index 28(DAS28) (both mRSS and DAS28 were evaluated by the same physician); erythrocyte sedimentation rate and C-Reactive Protein (CRP); Lung Function Tests (LFTs), ie. Forced Vital Capacity (FVC), and Diffusing Capacity for Carbon Monoxide (DLCO) corrected for hemoglobin. A decrease of >10% for FVC and/or >15% for DLCO of predicted values (according to the cutoffs set in the FocuSSed and FaSScinate trials) at the end of every year of treatment and at follow-up end was considered clinically significant. Additionally, physician global visual analogue scale (VAS) and patient reported outcomes including Scleroderma Health Assessment Questionnaire (SHAQ) and patient global VAS were recorded. Adverse events manifested during tocilizumab treatment were recorded for all patients.

Off-label use of tocilizumab 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 Student's t-test, respectively. Comparison of values before and after tocilizumab 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 values of $p<0.05$. All statistical analyses were performed in SPSS version 25.0.

Results

In total, 21 patients (20 women, 16 diffuse SSc, aged 52±10 years, disease duration 6.4±3.7 years) refractory to corticosteroids (n=21), methotrexate (n=19), cyclophosphamide (n=10), mycophenolate (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 co-existent RA or any other overlap syndrome and none had positive rheumatoid factor or anti-cyclic citrullinated antibodies. Ten patients had early disease (6 of them fulfilled also eligibility criteria for the FocuSSed and the FaSScinate trials) while 11 patients had long-standing disease. According to the EUSTAR MAI, all patients had active disease with a mean MAI of 5.1±1.8, mean mRSS of 21.5±9.5 and

mean DAS28 of 5.3±0.7, while 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 one year of tocilizumab treatment, while one patient withdrew after 3 months due to rapid disease deterioration. After the first year of treatment, 12 of 20 patients achieved low disease activity with a 3.0±1.9 decrease ($p<0.001$) in MAI, 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 (+2, -20)], four had no change and one patient deteriorated. Notably, individual baseline CRP serum levels correlated to decreases of mRSS ($r=0.583$, $p=0.012$). Moreover, 16 of 18 patients with joint involvement, 13 of 15 with polyarthritis and 3 with oligoarthritis, at baseline experienced clinical improvement which was also depicted in patients' reported outcomes as SHAQ was 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 more than 15% in 2 and remained stable in 18 patients. As shown in **Table 3** and in figures 1 and 2 in the Supplement, significant improvements after the first year of tocilizumab treatment were evident in MAI, mRSS, DAS28, ESR, CRP, SHAQ, patient and physician global VAS.

During the 2nd year of treatment, 3 of 20 patients discontinued tocilizumab due to adverse events or inefficacy and one 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 years), the remaining 16 patients on tocilizumab (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, while three patients (no 2, 6, and 18, **Table 2**) presented a decrease in FVC >10% compared to baseline. Individual changes in clinical and laboratory parameters at last follow-up visit are also depicted in figures 3, 4, 5 and 6 in the Supplement.

Safety

During tocilizumab treatment one patient developed severe cytomegalovirus infection manifested with fever and hepatitis but with no intestine involvement, leading to permanent treatment discontinuation. Additionally, 3 patients developed recurrent infection of digital ulcers resulting in temporary drug discontinuation and one hospital admission. Regarding laboratory abnormalities, no patient presented liver function tests above 1.5 times the upper normal limit, 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 prevalent in approximately 16% of SSc patients(21) and both these clinical manifestations, oftenly refractory to standard immunosuppressives, may lead to severe disability due to contractures and persistent synovitis..

An early EUSTAR observational study about the efficacy of tocilizumab 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 FocuSSed trial(17), examined the effect of tocilizumab on early diffuse cutaneous SSc. In both RCTs, the primary end-point of significant change in mRSS after 24- and 48-months treatment with tocilizumab, respectively, was not achieved compared to placebo. However, significant differences in exploratory and secondary end-points such as the significantly higher number of patients achieving the least clinically important decrease in mRSS in the FaSScinate trial and an mRSS improvement greater than 20% in the focuSSed trial, might support a potential beneficial effect of tocilizumab on skin thickening in some patients. Moreover, in both RCTs, tocilizumab treatment resulted in FVC stabilization compared to placebo, and in radiological stabilization in the focuSSed trial, suggesting an antifibrotic effect of tocilizumab in radiologically evident ILD(17).

In the present study we report the efficacy of tocilizumab 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 tocilizumab in such patients is lacking, as in both recent RCTs an important proportion of patients were DMARDs-naïve.

Analysis of our data showed significant clinical improvements after one year of tocilizumab treatment, as synovitis remitted in 80%, Mrss significantly decreased in 65% and low disease activity was achieved in 60% of our patients Importantly, in our cohort no patient fulfilled criteria for overlap RA or other rheumatic disease, thus precluding any confounding effect of overlap syndromes in our analysis. Accordingly, these clinical improvements were depicted in the functional status as SHAQ and patient global VAS were significantly improved. Moreover, tocilizumab treatment resulted in stabilization of FVC and DLCO in 80% of our patients, in accordance to the faSScinate and focuSSed trial results(16,17). Notably, the initial beneficial effect of tocilizumab on joint/skin and pulmonary involvement was preserved in the majority of patients after a mean treatment duration of more than two years, consistently to the results of the focuSSed trial in which tocilizumab 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 that would be ineligible for the faSScinate or the focuSSed trial, and 9 of these 11 patients had significant and sustained clinical improvement with tocilizumab. Since in both RCTs(16,17) all participants had early disease, this finding suggests that the efficacy of tocilizumab in SSc may be independent of disease duration.

Additionally, we observed that higher baseline CRP serum levels were associated with greater improvements of mRSS, consistently to the focuSSed trial results where tocilizumab 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 SSc patients have continuously elevated CRP throughout 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 tocilizumab treatment.

Finally, only 4 of 20 patients in our study had deterioration of lung function tests after the first year of tocilizumab treatment. Overall, the paucity of evidence regarding tocilizumab effect on visceral involvement, except the existing data from the FaSScinate and the FocuSSed trials, indicating a beneficial effect of tocilizumab 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 to 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 tocilizumab may be extended to the internal organs, resulting in better disease outcomes(24). Certainly, more RCTs

investigating the efficacy of tocilizumab in different clinical aspects of SSc are needed in order to establish tocilizumab as an approved treatment for SSc. The latter will facilitate its administration in SSc patients, which currently in most countries due to its high cost and limited clinical experience is only administered off-label and after approval from national committees. Notably, very recently tocilizumab has been approved by the FDA for the treatment of SSc-ILD.

Regarding safety, one patient developed cytomegalovirus infection enforcing permanent tocilizumab withdrawal, while 3 patients had recurrent infected digital ulcers requiring temporary drug discontinuation. The development of digital ulcer infections and subsequent osteomyelitis in a limited number of patients was also reported in FaSScinate and focuSSed, raising special 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, the inclusion of different SSc subtypes allowing to test the efficacy of tocilizumab in patients with different disease characteristics, and the long-term follow-up. All our patients were Caucasian 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 tocilizumab.

A main limitation of the present study is the lack of a blinded assessor for mRSS and joint count which may have influenced 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 tocilizumab, especially regarding patients with long-standing disease for whom a spontaneous regression due to a self-limiting course of the disease is possible. However, the fact that our patients with long-standing disease had persistently high disease activity despite prolonged immunosuppression and improved soon after tocilizumab administration supports the beneficial effect of tocilizumab in these patients. Accordingly, data regarding patients' RNA polymerase III antibody status, a predictor of severe skin sclerosis, was unavailable and did not allow us to identify patients more likely to have spontaneous regression of skin thickening. Regarding pulmonary assessment, as serial chest computed tomographies were not available for all patients, we could not confirm that the functional stability observed was consistent to radiological stabilization in our patients.

In conclusion, our results showed that tocilizumab 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, irrespective 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.

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Supplemental figure 1. Mean change of clinical parameters, including modified Rodnan skin score (mRSS), Disease activity score 28 (DAS28), modified activity index (MAI), number of tender joints and number of swollen joints in 20 patients with Systemic Sclerosis, after the first year of treatment with tocilizumab.

Supplemental figure 2. Mean change of laboratory parameters, including Forced Vital Capacity (FVC, % of predicted), Diffusing Lung capacity for Carbon Monoxide (DLCO, % of predicted), C-reactive protein (CRP, mg/l) and Erythrocyte Sedimentation Rate (ESR, mm/1st hour) in 20 patients with Systemic Sclerosis, after the first year of treatment with tocilizumab.

Supplemental figure 3. Individual values of modified Rodnan skin score (mRSS) at baseline (initiation of tocilizumab treatment) and at last follow-up visit in 21 patients with Systemic Sclerosis treated with tocilizumab (mean duration of tocilizumab treatment 2.2±1.1 years)

Supplemental figure 4. Individual values of Disease activity score 28 (DAS28) at baseline (initiation of tocilizumab treatment) and at last follow-up visit in 21 patients with Systemic Sclerosis treated with tocilizumab (mean duration of tocilizumab treatment 2.2±1.1 years)

Supplemental figure 5. Individual values of Forced Vital Capacity (FVC) at baseline (initiation of tocilizumab treatment) and at last follow-up visit in 21 patients with Systemic Sclerosis treated with tocilizumab (mean duration of tocilizumab treatment 2.2±1.1 years)

Supplemental figure 6. Individual values of C-reactive protein (CRP) at baseline (initiation of tocilizumab treatment) and at last follow-up visit in 21 patients with Systemic Sclerosis treated with tocilizumab (mean duration of tocilizumab treatment 2.2±1.1 years)

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

No	Sex/ Age	Type/Major organ involvement	Autoantibodies	Disease duration (years)	Prior IMS *(duration of treatment in months)	MAI	mRSS	ESR/CRP	Joint count (T/S)	DAS-28	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	limSSc/ 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	limSSc/ 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	limSSc/ -	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	limSSc/ -	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	limSSc / -	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

dc: diffuse; lim: limited; RF: rheumatoid factor; CCP: cyclic citrullinated peptide; ANA: antinuclear antibodies; ENA: extracted nuclear antibodies (including anti SSA, anti-SSB, anti-Sm, anti-RNP, anti-Jo1, Anti-Topoisomerase); Topo: Topoisomerase 1; IMS: immunosuppressive; MAI: modified activity index; mRSS: modified Rodnan skin score; ESR: erythrocyte sedimentation rate (mm/1st hr); CRP: c-reactive protein (mg/l); T: tender; S: swollen; DAS: disease activity score; SHAQ: scleroderma health assessment questionnaire; FVC: forced vital capacity; DLCO: diffusing capacity for CO; AE: adverse event; D/Us: digital ulcers PF: pulmonary fibrosis; HI: heart involvement; RC: renal

crisis; Cs: corticosteroids; CYC: cyclophosphamide; HCQ: hydroxychloroquine; HSCT: autologous hematopoietic stem cell transplantation; LEF: leflunomide; MMF: mycophenolate mofetil; MTX: methotrexate; RTX: rituximab.

Table 2. Individual clinical Outcomes at last follow up visit (mean duration of tocilizumab treatment 2.2±1.1 years) of 21 patients with Systemic sclerosis treated with tocilizumab

No	TCZ tx duration (mo)	Concomitant treatment *(dose in mg)	mRSS (change from baseline)	FVC / DLCO (% of predicted) (change from baseline)	Joint Count (T/S)	ESR/CRP	DAS28 (change from baseline)	SHAQ (change from baseline)	Treatment status	AEs
1	3	Prz (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) + Prz (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	Prz (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	Prz (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	D/U infection
8	16	Prz (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) + Prz (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	Prz (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) + Prz (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	Prz (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	Prz (7.5)	21 (0)	52 (-12)/ 36 (-11)	10 / 4	7 / 0.1	4.3 (-1.8)	1.8 (-0.8)	ongoing	D/U infection
19	45	Prz (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	Prz (5)	18 (-8)	54 (-4) / 44 (+2)	4 / 1	8 / 1.4	3.2 (-2.7)	0.1 (-0.5)	ongoing	D/U infection

tx: treatment; mo: months; mRSS: modified Rodnan skin score; DAS: disease activity score; SHAQ: scleroderma health assessment questionnaire; FVC: forced vital capacity; DLCO: diffusing capacity for CO; T: Tender; S: swollen; ESR: erythrocyte sedimentation rate (mm/1st hr); CRP: c reactive protein (mg/l); AE: adverse event; D/Us: digital ulcers; CMV: cytomegalovirus; Prz: prednisolone; Mp: methylprednisolone; MTX: methotrexate; TCZ: Tocilizumab; d/c: discontinuation;

Table 3. Clinical and laboratory parameters and measures (mean ± SD) at baseline and after one year of treatment with tocilizumab in 20 patients with Systemic Sclerosis

	Baseline	1st year	change	p
Modified activity index	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 (% of predicted)	82 ± 19.5	79 ± 19.1	-2.9 ± 12	0.389
DLCO (% of predicted)	60.4 ± 16.3	61.1 ± 18.4	0.7 ± 12.3	0.844
ESR (mm/1st hr)	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**
VAS patient global score (0-100)	37.8 ± 16.8	60.5 ± 15.4	22.7 ± 20.3	**<0.001**
VAS physician global score (0-100)	33.4 ± 13.2	63.2 ± 13.9	29.8 ± 15.6	**<0.001**

mRSS: modified Rodnan skin score; DAS28: disease activity score 28; FVC: forced vital capacity;
DLCO: diffusing lung capacity for carbon monoxide; ESR: erythrocyte sedimentation rate;
CRP: c-reactive protein; SHAQ: scleroderma health assessment questionnaire; VAS: visual analogue scale