Long-Term Follow-Up of Patients with Scleroderma Interstitial Lung Disease Treated with Intravenous Cyclophosphamide Pulse Therapy: A Single-Center Experience

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ABSTRACT: **Background:** Scleroderma lung disease (ILD-SSc) is treated mainly with cyclophosphamide (CYC). The effectiveness of CYC was judged after 12–24 months in most reports.

Objectives: To analyze the effect of monthly intravenous CYC on pulmonary function tests including forced vital capacity (FVC) and diffusing lung capacity (DLCO), as well as Rodnan skin score (mRSS), during long-term follow-up.

Methods: We retrospectively collected the data on 26 ILD-SSc patients who began CYC treatments before 2007. Changes in FVC, DLCO and mRSS before treatment, and at 1, 4 and 7 years after completion of at least six monthly intravenous CYC treatments for ILD-SSc were analyzed.

Results: Mean cumulative CYC dose was 8.91 ± 3.25 G. More than 30% reduction in FVC (0%, 8%, and 31% of patients), DLCO (15%, 23%, 31%), and mRSS (31%, 54%, 62%) at years 1, 4 and 7 was registered. During the years 0–4 and 4–7, annual changes in FVC, DLCO and mRSS were 3.2 vs. 0.42% ($P < 0.040$), 4.6 vs. 0.89% ($P < 0.001$), and 1.8 vs. 0.2 ($P = 0.002$). The greatest annual FVC and DLCO reduction over the first 4 years correlated with mortality ($P = 0.022$). There were no differences in the main variables regarding doses of CYC (< 6 G and > 6 G).

Conclusions: In patients with ILD-SSc, CYC stabilized the reduction of FVC during treatment, but this effect was not persistent. The vascular characteristic of ILD-SSc (DLCO) was not affected by CYC treatment. CYC rapidly improved the mRSS. This effect could be achieved with at least 6 G of CYC. Higher rates of annual reduction in FVC and DLCO in the first 4 years indicate the narrow window of opportunity and raise the question regarding ongoing immunosuppression following CYC infusions.

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KEY WORDS: systemic sclerosis (SSc), interstitial lung disease (ILD), pulmonary function tests, modified Rodnan skin score (mRSS), cyclophosphamide (CYC)

Interstitial lung disease (ILD) associated with systemic sclerosis (SSc, ILD-SSc) may result in severe morbidity and mortality. Severe ILD has been reported in about 16% of SSc patients; ILD has accounted for 21.5% of all deaths in SSc patients and for 44% of the deaths related to SSc. Treatment regimens for ILD-SSc include the use of various drugs, such as corticosteroids (Cs), cyclophosphamide (CYC) – either intravenous (IV-CYC) or oral (Or-CYC), azathioprine (AZA), mycophenolate mofetil (MMF) and, recently, biological agents. Among the drugs used only CYC has been assessed in randomized controlled trials (RCT) [1,2]. In the last decade several reports on the use of CYC in the treatment of ILD-SSc have been published [Table 1] [3-21]. CYC was typically used for 6–12 months, and in the majority of reported studies its efficacy and safety issues were determined after 12–24 months of follow-up; long-term follow-up results were reported only in some [3,15,16,19]. Amelioration of skin fibrosis was mentioned in some of these reports. The aim of the present study was to analyze changes in pulmonary function tests (PFT) and skin thickening as measured by modified Rodnan skin score (mRSS) in patients treated with IV-CYC for ILD-SSc during long-term follow-up (up to 4 and 7 years).

PATIENTS AND METHODS

The study was performed at the B. Shine Rheumatology Unit of Rambam Health Care Campus, a tertiary and medical faculty-affiliated hospital in northern Israel. The majority of patients registered at our EUSTAR (EULAR Scleroderma Trials and Research group) site (042) undergo annual clinical and laboratory assessment according to Medical Essential Data Sheets. Patients with potential pulmonary involvement or established pulmonary disease undergo regular (every 1–3 months) clinical and PFT assessment in the Fibro-Vascular Clinic, which is run by an SSc expert rheumatologist and pulmonologist. High reso-

Table 1. Results of studies on the use of cyclophosphamide for scleroderma-associated lung disease

Author Year [ref]	Type of study	No. of patients	Route of treatment	Treatment period (months)	Overall outcome	Lung function tests	Follow-up (months)	Overall outcome	Lung function tests
Silver 1993 [11]	Open	14	Or-CYC + Cs	6	–	Improved	12–18–24	–	Stable
Akisson 1994 [20]	Open	18	Or-CYC+Cs	12	Improved	Improved	–	–	–
Steen 1994 [12]	Retrospective	14	Or-CYC and IV-CYC	6	–	Improved	–	–	–
Davas 1999 [6]	Randomized unblinded	8+8	IV-CYC+Cs Or-CYC+Cs	12	Improved	Improved	6–12	–	Improved
White 2000 [7]	Open	39	35 Or-CYC 4 IV-CYC	12 6–9	Improved	Improved	17–36 (mean 22)	Improved	Improved
Pakas 2002 [10]	Open label non-parallel arm	12 16	IV-CYC + l/d Cs IV-CYC+ h/d Cs	12	Improved	Stable Improved	–	–	–
Giacomelli 2002 [13]	Open	23	IV-CYC+Cs	6	Improved	Stable Improved	–	–	–
Griffiths 2002 [14]	Open	14	IV-CYC + IV Cs	6	Improved	Stable Improved	12 26	–	Stable Deteriorated 67%
Nadashkevich 2006 [5]	Randomized unblinded	30	Or-CYC+Cs	12	Improved	Stable	18	Improved	Stable
Tashkin 2006 [1]	RCT	158	Or-CYC	12	Improved	Improved	24	Stable	Stable
Hoyles 2006 [2]	RCT	45	IV-CYC+Cs followed AZA	6	–	Stabilized	12	–	Stable
Beretta 2007 [8]	Open	33	Or-CYC+Cs	12	–	Improved	12	–	Stable
Airò 2007 [9]	Open	13	IV-CYC+IV Cs	6+4 (quarterly)	–	Improved	18	–	Improved 4 Stable 2
Mittoo 2007 [15]	Open	25	Or-CYC+/- Cs	6	Stable	Stable	18 (41–57)	Stable	Stable
Yiannopoulos 2007 [19]	Open	13	IV-CYC+IV Cs	24	–	Improved	6,12,18,24,48		Improved
Simeón-Aznar 2008 [17]	Prospective observational study	10	IV-CYC+Cs	6+3 (bimonthly)	–	Stable Improved	24	–	Stable 5 Improved 5
Bérezné 2008 [18]	Open	27	IV-CYC+Cs followed AZA	6	–	Improved/ stable 70%	24		Improved/ stable 51.8%
Tochimoto 2011 [3]	Open	13	IV-CYC+Cs	2–6	–	Improved	12–48	–	Stable 7
Gonzalez-Nieto 2011 [4]	Open	5	IV-CYC+Cs followed MMF	6+19 (quarterly)	Unstable	Stable	24	Improved	Improved
Domiciano 2011 [16]	Prospective open-label controlled	18	IV-CYC+/-Cs	12	Improved	Stable	36	Stable	Stable
Espinosa 2011 [21]	Retrospective	37	IV-CYC + Cs	6-24	–	Stable	24	–	Stable

Or-CYC = oral cyclophosphamide , Cs = corticosteroids, IV-CYC= intravenous cyclophosphamide, l/d = low dose, h/d = high dose, AZA = azathioprine, MMF = mycophenolate mofetil

lution chest computed tomography (HRCT) scans are regularly revised by a CT expert at the staff meetings of our pulmonary imaging and rheumatology unit. For patients with reduced PFT or signs of heart or respiratory failure, serial cardiac echocardiography Doppler (ECHO) is performed according to clinical judgment. All patients registered in the EUSTAR database at our center fulfilled the LeRoy Scleroderma classification [23].

We included in the study only data on patients with ILD-SSc who had been treated with IV-CYC (no patients were treated with Or-CYC at our center). Patients were treated with IV-CYC if they had symptoms (cough, dyspnea, lung crepitus) and one of the changes on HRCT and/or PFT listed below:

- Presence of ground-glass opacities and/or pulmonary fibrosis and/or honeycomb cysts and/or traction bronchiectasis on chest HRCT
- Reduced functional vital capacity (FVC) and/or diffusing capacity of lung for carbon monoxide (DLCO) less than 75% of predictable value

- Reduction in FVC and/or DLCO of more than 10% on two consecutive visits

Patients' data were extracted from the EUSTAR database at our site and from medical records since 2004 with data cut at 2012. Data on patients who were treated with CYC before 2004 were obtained from medical records. Patient demographic data included age, gender, and disease duration from the first non-Raynaud's phenomenon symptom. Clinical data included SSc subsets [diffuse (DcSSc) or limited (LcSSc)], cough, dyspnea, lung crepitus, results of HRCT, FVC and DLCO, and data on pulmonary artery pressure (PAP) assessed by Doppler echocardiography. Laboratory data included autoantibody status [antinuclear antibodies, anti-topoisomerase (ATA), and anti-centromere (ACA)], levels of serum creatinine and creatinine kinase (abnormal CK > 1.5 of normal limits). For patients who died during the follow-up period, the date and cause of death were recorded.

Treatment with monthly pulses of IV-CYC at a dosage of 0.6G/M2 (750–1400 mg per treatment in the individual patient) was performed on inpatient admission every 4 weeks for at least six cycles. All patients received premedication with IV granisetron or ondansetron, 4 mg dexamethasone, and MESNA at the same dosage as CYC (divided into two doses before and after IV-CYC). Prior to every IV-CYC treatment, patients underwent laboratory tests for complete blood count and serum creatinine. Data on FVC, DLCO and mRSS before treatment and at years 1, 4 and 7 after completion of IV-CYC were analyzed. PFT reduction was categorized into three subgroups: mild (< 10%), moderate (10% < 29%), severe (> 30%). Reduction in mRSS of more than 30% was defined as essential and was analyzed separately. Changes in PAP were recorded as well.

For statistical analysis, Student's paired *t*-test, Mann-Whitney U-test, and Wilcoxon Signed Ranks tests were used ($P < 0.05$ was defined as significant).

RESULTS

Between January 2004 and December 2012, of the 170 SSc patients registered at our site, 38 (21.8%) had symptomatic ILD; 26 patients who started IV-CYC before 1 January 2007 were eligible. In the whole group there were 17 patients who started IV-CYC before 1 January 2004 and had a follow-up for 7 years at least. Patients' demographic and clinical data are presented in Table 2. Sixteen patients received an additional immune-suppressive drug after finishing IV-CYC treatment [11 AZA, 2 methotrexate (MTX) and etanercept (in one of them, treatment was switched from MTX to MMF), 2 MMF, 1 etanercept, 2 rituximab]. All patients were initially treated with 10 mg prednisolone daily, 10 succeeded in tapering off steroids; the rest were on different prednisone doses (5–10 mg/day).

The proportion of patients with mild, moderate, or severe FVC and DLCO reduction during year 1, 4, and 7 of follow-up is presented in Figure 1. There were no patients with severe reduction in FVC after 1 year; severe reduction in DLCO after 1 year had already been observed in 15% of the patients.

One year after starting IV-CYC, the mean FVC was 75.7% (SD 18.4) of the predicted value; the reduction was not significant ($P < 0.08$) when compared to initial FVC levels. In contrast, DLCO was low already at the start of IV-CYC and had reduced significantly from initial values (55.5%, SD 12.9, $P < 0.008$) at the end of the first year of follow-up. Data on mean (SD) values of FVC and DLCO at time points 0, and years 1, 4 and 7 and their comparisons are presented in Figure 2. Differences between variables at the end of year 7 compared to year 1 were significant regarding FVC and DLCO ($P < 0.015$ and 0.002, respectively; 13 patients). Annual changes in FVC and DLCO during the first 4 years (26 patients) and the next 3 years (17 patients) were as follows: annual FVC reduction 3.2% and 0.42% ($P < 0.04$), annual DLCO reduction 4.6% and 0.89% ($P < 0.001$). Annual rate of reduction in PFT during year 1 of follow-up, between year 1 and 4, and between year 4 and 7 of follow-up were not significant (Wilcoxon Signed Ranks Test, paired).

Table 2. Demographic and clinical data before starting cyclophosphamide

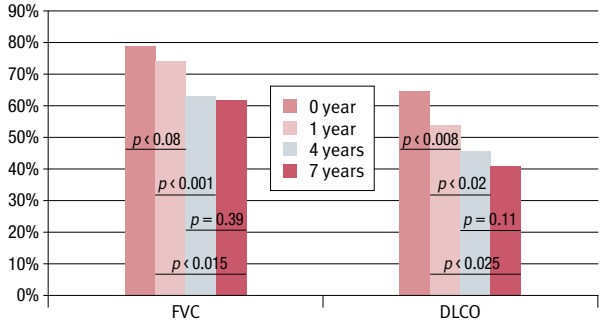
No. of patients treated with CYC	26
Age (years) mean (SD)	50.7 (12.7)
Female (%)	20 (77)
Disease duration (months), mean (SD)	16.3 (17.9)
Follow-up (years) mean (SD, range)	6.5 (6) (3–11)
DcSSc (%)	15 (58)
Antibodies: ANA (%)/ATA (%)	25 (96.2)/20 (77)
Creatine kinase elevation (%)	8 (31)
Cough	16 (62)
Dyspnea	23 (88)
Lung crepitus	19 (73)
Ground-glass opacities	1 (4)
Ground glass opacities and pulmonary fibrosis	21 (81)
Pulmonary fibrosis	4 (15)
FVC (%), mean (SD)	81.5 (17.2)
DLCO (%), mean (SD)	67.1 (13.0)
mRSS, mean (SD)	14.5 (11.6)
Estimated PAP, mmHg; mean (SD)	33.3 (8.6)
Cumulative CYC dose (g), mean (SD) Median (minimal-maximal)	8.91 (3.25) 8 (5–17)
Dead (%) First 4 years (%)	8 (28.6) 2 (7.1)

CYC = cyclophosphamide, SD = standard deviation,DcSSc = diffuse cutaneous systemic sclerosis, ANA = antinuclear CYC = cyclophosphamide, SD = standard deviation, ANA = antinuclear antibody, ATA = anti-topoisomerase, FVC = forced vital capacity, DLCO = diffusing capacity of lung for carbon monoxide, mRSS = modified Rodnan skin score, PAP = pulmonary artery pressure

Figure 1. [A] The proportion of patients with FVC and DLCO reduction during follow-up

FVC = functional vital capacity, DLCO = diffusing capacity of lung for carbon monoxide

Figure 2. Dynamic changes in FVC and DLCO during follow-up



FVC = functional vital capacity, DLCO = diffusing capacity of lung for carbon monoxide

Mild improvement in mRSS was observed in 46% of patients after 1 year of IV-CYC treatment, and in 23% and 15% of patients after 4 and 7 years, respectively. More than 30% of the initial mRSS reduction was registered in 31% of patients after year 1, and 54% and 62% of patients after years 4 and 7, respectively. mRSS dropped from 14.6 (SD 11.7, 18 patients) to 11.0 (SD 8.6, 18 patients) at the end of year 1 ($P < 0.005$) to 6.8 (SD 4.2, 18 patients, $P < 0.001$) at year 4, and 5.3 (SD 3.2, 18 patients, $P < 0.06$) at year 7. Annual changes in mRSS during the first 4 years (26 patients) and the subsequent 3 years (17 patients) were significant (1.8 and 0.2, P = 0.002). The annual rate of reduction in mRSS was significant in the first 4 years ($P < 0.001$); the annual rate of mRSS reduction was non-significant in the next 3 years ($P < 0.08$).

Estimated PAP remained almost unchanged in 92% of patients at year 1. The proportion of patients with severe elevation of PAP (> 30%) remained about 8% during follow-up. Variables such as gender, disease duration, disease subset, presence of ATA, cough, dyspnea, lung crepitus, weight loss, and the presence of digital ulcers did not predict severe reductions in FVC and/or DLCO (> 30%) in the subsequent 7 years. Elevated CK before initiation of IV-CYC correlated with a higher annual reduction in FVC ($P < 0.04$) and annual reduction in DLCO ($P < 0.026$) during the first 4 years of follow-up. Higher initial mRSS correlated with total FVC reduction after 7 years ($P < 0.017$).

There was no significant difference between total and annual FVC and DLCO reduction in terms of different IV-CYC doses (6G for 7 patients and > 6G of CYC for 18 patients) in the first year of treatment; changes in mRSS showed a tendency for reduction but did not reach significance regarding the total CYC dose ($P < 0.063$).

Two patients had an overlap of SSc and severe rheumatoid arthritis and were treated with etanercept; both patients showed severe decline in FVC and DLCO and developed severe pulmonary artery hypertension (PAH) and congestive heart failure at the end of follow-up. Two SSc patients received rituximab for ILD-SSc (one patient once, one patient twice; there was no further deterioration in PFT in either case). Unfortunately, one of these patients died due to sepsis 6 months after rituximab and 2 years after completing CYC treatment.

In general, there were no reactions during IV-CYC infusions; five adverse events were registered in three patients. In one, hepatitis B reactivation responded to lamivudine; this patient later developed ankle Kaposi sarcoma that resolved after discontinuation of CYC (this patient had received 17G CYC). Another patient developed pneumonia that responded to antibiotics, and another patient had premature menopause (12G CYC). There were no cases of leukopenia or neutropenia on repeated blood tests.

Eight patients died during follow-up (30.8%): 3 (37.5%) due to respiratory failure and PAH and 5 from non-pulmonary causes (1 had renal crisis during CYC treatment, 1 suffered acute myocardial infarction 1 year after discontinuation of CYC, 1 had pancreatic cancer 3 years after CYC treatment, 1 had sepsis 2 years after CYC treatment, and 1 had intestinal perforation 4 years after CYC treatment). Six deceased patients had severe FVC and/or DLCO reduction; there were no statistically significant differences between the last FVC of the surviving and deceased patients (63% and

57%, $P = 0.2$). Severe reduction in FVC showed only a slight tendency for mortality ($P = 0.08$), while the highest annual reduction in FVC during 4 years of follow-up correlated with mortality ($P = 0.022$). Severe reduction in DLCO and highest annual reduction in DLCO during 4 years of follow-up correlated with mortality ($P = 0.013$, 0.022).

DISCUSSION

Early reports on the use of CYC for ILD-SSc in small open studies [5-7,10-14,20] were quite optimistic. Later, in a scleroderma lung study [1], treatment with Or-CYC for 1 year with follow-up for the second year resulted in a significant though modest improvement in FVC and better functional capacity. In another RCT with IV-CYC for 6 months followed by AZA for another 6 months, stabilization of FVC was demonstrated at the end of the study period [2]. As a result of RCTs and the increased number of reports on the use of CYC in open series, this drug has become a main agent in the short-term management of ILD-SSc.

According to the European League against Rheumatism (EULAR) and EUSTAR recommendations published in 2009, CYC should be considered for the treatment of ILD-SSc. The EUSTAR guidelines also emphasized the potential risk of CYC therapy [23].

To date, only a few reports have been published on the long-term effects of CYC. Yiannopoulos et al [19] reported on 13 patients treated with IV methylprednisolone and prolonged IV-CYC treatment. After 48 months of follow-up, 66.7% of the patients had stable or improved FVC and 58.4% had stable or improved DLCO [19]. Tochimoto and co-authors [3] reported on 48 months of follow-up of 13 ILD-SSc patients treated with IV-CYC: 7 patients reached the 48 month point with no recurrence of alveolitis [3].

The present study is a retrospective analysis of 26 patients with relatively long follow-up – 4 years at least, and 7 years in some (17 cases). Treatment results 1 year after starting IV-CYC therapy in our patients were more or less similar to the existing evidence that CYC treatment may stabilize FVC but does not have much impact on DLCO. Our main interests were changes in FVC and DLCO in the years following CYC treatment, as well as dynamic changes in these variables (annual reduction and the rate of reduction). Regarding FVC, a significant proportion of patients (approximately 60%) demonstrated continuous and progressive impairment in lung volumes after discontinuation of IV-CYC treatment at year 4 and 7; in approximately 30% of patients the reduction was severe. The main changes in FVC, the highest annual reduction and the rate of FVC reduction were registered in the first 4 years of ILD-SSc. Changes in DLCO were already more prominent after 1 year of follow-up and continued to decline in the subsequent years, again with a non-significant but higher annual reduction and reduction rate in the first 4 years. Based on these data we suggest that IV-CYC probably realizes its suppressive effect on the inflammatory component in the interstitium with no impact on pulmonary vasculature. Regarding the annual rate changes in FVC and DLCO, it was obvious that these were lowest during active IV-CYC treatment than in subsequent years. The discrepancy in the rates and the severity of FVC and DLCO deterioration after stopping IV-CYC probably indicates uncontrolled silent inflammation and fibrosis progression as well. The proportion of our patients treated with another immune-modulatory drug after discontinuation of IV-CYC was too small to allow comparison with patients who were treated with IV-CYC alone, or to draw conclusions.

Our results confirm the existing data that in ILD-SSc patients treatment with IV-CYC may have a place as an induction therapy. High doses of IV-CYC in our patients did not add to the success of treatment but were accompanied by side effects. We suggest that the dosage of 6G of IV-CYC may be sufficient for induction therapy of ILD-SSc.

We demonstrated that after discontinuation of IV-CYC there was further reduction in PFT; this fact raised the question regarding the need for maintenance therapy for ILD-SSc after discontinuation of induction treatment with CYC. According to a three-step survey of 117 SSc experts from the EUSTAR group, active ILD-SSc treatment with IV-CYC is recommended (options such as MMF or AZA were also suggested); three-fourths of the experts agreed that maintenance therapy is an important issue and preferred MMF for this indication. EUSTAR recommendations also considered CYC for the treatment of ILD-SSc (with careful follow-up of toxicity), with preference for the use of intermittent IV pulses (6–18) in doses ranging from 0.5 to 2 g/m^2) per pulse [24].

Who are those ILD-SSc patients who should be treated more aggressively? In a group of 330 patients with ILD-SSc, Goh et al. [25] reported that the negative impact on mortality was related to the extent of reticular infiltrates on chest HRCT (more than 20%) and significant reduction in FVC (< 70% of predicted). Our patients had HRCT changes compatible with ILD-SSc, but that did not address the degree of HRCT changes in this study. According to our results, the highest annual reduction and the rate of reduction in FVC and DLCO in the first 4 years corresponded to the worst outcome. This indicates that dynamic changes in FVC and DLCO are important in discerning which patients will need frequent evaluation and prompt treatment. Another clue in our results is the fact that patients with the highest mRSS and/or elevated CK levels developed maximal reduction in FVC at the end of the follow-up period.

All our patients had short disease duration before IV-CYC treatment, so we can speculate that they had no "late" pulmonary changes. But even in this group of patients with early lung involvement there was a progressive reduction in PFT.

This fact strengthens the notion that pulmonary fibrosis has additional stimulatory pathways other than inflammation. Disproportionally early reduction in DLCO probably indicates that fibrotic (and vascular) changes may appear in the very early SSc stages. In this situation, even aggressive treatment such as IV-CYC may have limited impact on this aspect of disease progression.

According to our findings, the behavior of lung and skin pathology in SSc is not identical. The mean mRSS in our patients was obviously less than in RCTs (approximately 21.0–27.3), and only about half our patients had DcSSc. According to data from RCTs, the main changes in mRSS occurred in patients with more than 24 months of disease duration, and the most prominent reduction in mRSS occurred in patients with long disease duration and after 24 months. Mean disease duration in our group was 16.3 months. In contrast to published data from RCTs, a significant reduction in mRSS and the highest rate of skin thickness reduction had already been registered during the first year of therapy and remained high over the next 3 years (from year 1 to 4). Regarding skin thickness, we can conclude that IV-CYC rapidly and persistently improved mRSS.

In general, all variables changed more during years 1–4 of follow-up relative to the next 3 years. This probably means that in treatment of ILD-SSc the window of opportunity is very narrow. Early recognition of patients with potentially progressive lung disease (extended HRCT changes, higher mRSS, high CK, reduced baseline DLCO, rapid reduction in FVC and DLCO) and more comprehensive efforts in assessing and treating may affect the disease course.

Our study has several limitations. It is a retrospective study; the number of patients who reached 7 years post-IV-CYC treatment is small (the whole group was relatively small); the group was heterogeneous (some patients were treated only with IV-CYC and some with additional immunosuppression, mostly in recent years); and there was no control group (not even "historical"). Despite these limitations, we could present an analysis of patient data for 4 and 7 years after CYC treatment. In the absence of long-term outcome data on patients with ILD-SSc, our results may be helpful.

CONCLUSIONS

In patients with ILD-SSc, IV-CYC stabilized the reduction of lung volumes under treatment, but this effect was not persistent. The vascular characteristic of ILD-SSc (DLCO) was not affected by IV-CYC treatment. Higher CYC doses (more than 6G total) do not necessarily have an additional impact on the course of ILD-SSc. Further deterioration of PFT in the years subsequent to IV-CYC treatment (< 4 years) raises the question regarding the need for maintenance therapy. Treatment with IV-CYC had a rapid and prominent impact on skin thickening. The first 4 years in the course of active ILD-SSc are critical; the determination of treatment efficacy in this subgroup of patients (regarding lung and skin involvement) in a short time period (12–24 months) does not necessarily reflect the dynamic changes in main disease parameters in the subsequent years. In our data, dynamic (annual) changes in PFT reflected disease progression and correlated with the outcome (PFT reduction, mortality). In ILD-SSc patients, the severity and spread of skin thickening and elevated CK levels predicted the worst reductions in FVC and DLCO. Close and frequent assessment, and long-term follow-up with analysis of annual dynamic changes in FVC and DLCO may highlight a more severe condition and justify searching for more effective treatment.

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