Determinants of pulmonary function improvement in patients with scleroderma and interstitial lung disease

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Abstract

Background

In patients with scleroderma-related interstitial lung disease (ILD), improvements of pulmonary function have been reported after treatment with cyclophosphamide (CYC) alone or CYC and high-dose steroids. The study objective was to identify therapeutic regimen that alone or in combination with laboratory or clinical characteristics were associated with pulmonary function improvement in these patients.

Methods

Scleroderma patients with ILD and serial pulmonary function measurements were retrospectively analyzed. We recorded forced vital capacity (FVC, % predicted), diffusion capacity (DLCO, % predicted), type of therapy, and various clinical and laboratory parameters. Treatment with IV CYC was recorded as cumulative dose (grams) and treatment with steroids as high or low dose; outcome was defined as a sustained increase in FVC (% predicted) ≥ 10 points.

Results

Of the 59 patients who were included in the study, 29 (49 %) patients received IV CYC (cumulative dose 13.9 ± 6.2, range 5.2-26.2 gr) for 3.3 ± 2.4 years (range 5-60 months). Eighteen out of 59 (30 %) patients received high-dose prednisolone and 41 (70 %) received low-dose prednisolone. In an ordinal logistic model, patients receiving > 12 gr of CYC were 6 times more likely to improve FVC than to decrease or maintain FVC, compared to those who did not receive CYC ($p = 0.02$). In multivariate analysis, the effect of high dosage CYC on FVC persisted (OR 10.82, $p = 0.02$). Steroid dosage (high or low) was not associated with FVC improvement ($p < 0.05$).

Conclusion

In patients with scleroderma and ILD, treatment with CYC is the only variable that is independently associated with pulmonary function improvement and that prolonged (> 1 year) CYC therapy increases the probability of pulmonary function improvement more than shorter CYC courses.

Key words

Scleroderma, cyclophosphamide, pulmonary function, interstitial lung disease, pulmonary fibrosis.

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Introduction

In patients with systemic sclerosis (SSc), interstitial lung disease (ILD) is one of the major causes of death (1-5). Improvements of pulmonary function in these patients are predominantly linked to treatment with cyclophosphamide (CYC). The initial uncontrolled studies have shown that therapy with CYC may improve pulmonary function, or at least stabilize pulmonary fibrosis, as assessed by serial measurements of forced vital capacity (FVC) and diffusion capacity (DLCO) (6-16). In general, the FVC and DLCO improvements were in the range of 2-10%, lasting for a period of approximately 6 to 12 months following therapy discontinuation (6, 10-13, 17).

Recent randomized controlled trials using oral CYC for one year (13, 18) or IV CYC for six months (19) in patients with SSc and ILD confirmed the modest improvements of FVC and total lung capacity (TLC). In addition to CYC, improvements of pulmonary function were also associated with the use of steroids, especially when high dose steroids were combined with IV CYC (13). Finally, spontaneous improvements of pulmonary function have been described in a significant portion of untreated patients (18).

The present study aimed to verify whether specific therapeutic regimen alone or in combination with baseline laboratory or clinical characteristics could be associated with pulmonary function improvement in patients with SSc and ILD. We included a relatively large number of SSc patients treated at the same center with IV pulses of CYC and recorded the cumulative CYC dosage each patient received. Because duration of CYC therapy often exceeded one year, we specifically attempted to determine whether pulmonary function improvements were associated with cumulative CYC dosages.

Methods

Patients with diagnosis of SSc attending the University Rheumatology clinic at the University of Athens Medical School were identified and their charts were retrospectively reviewed. In all patients the diagnosis of SSc was made according to standard classification criteria (20). Patients were included in the study if they were followed up in our outpatient clinic for at least 3 years and had serial pulmonary function measurements, at least twice over the study period. Patients with a coexisting cardiac or neuromuscular disease were excluded. For the purpose of this study, onset of SSc was defined as the appearance of first skin manifestations other than Raynaud's phenomenon.

In all patients, we recorded FVC (% predicted) and single breath DLCO (% predicted) measurements, presence of antibodies (anti-Topoisomerase I), disease duration, and type of treatment. For patients treated with IV CYC, baseline pulmonary function measurements were those measured just prior to treatment initiation whereas for patients not treated with CYC were the first available. Treatment with IV CYC was recorded as the total dose (in grams) administered. CYC toxicity was assessed according to World Health Organization criteria (21).

The individual dose of intravenous CYC pulse ranged from 0.5 to 1.5 grams and was combined with oral steroids in different doses. The decision to initiate treatment with IV CYC was based on development of respiratory complaints (dyspnea), evidence of pulmonary function decline (FVC < 80 % predicted and/or DLCO< 70% predicted) in conjunction with presence of ILD on thoracic CT. Bronchoalveolar lavage analysis was not used to institute treatment in our patients. Depending on the initial steroid dose, patients treated with CYC were categorized into two separate groups: those who received low dose steroids from the beginning (< 10 mg prednisolone per day) and those who initially received high dose of prednisolone (approximately 1mg/kgr body weight/day) followed by gradual tapering. The CYC protocol included monthly pulses of IV CYC at a dosage of 1 gr/m^2 body surface for a period of 6 months, followed by bimonthly pulses for an additional period of 6 months. After this period, the IV pulses were given at longer intervals, approximately every three to four months.

Spirometry was performed according to standard techniques, using a spirometer (Masterlab; Jaeger, Wurzburg, Germany). Lung diffusion capacity for carbon monoxide (DLCO) was determined with the single breath method.

Data analysis

Ordinal logistic regression was used to assess potential association of various parameters and pulmonary function improvement. The outcome variable of interest was an ordered category defined as sustained improvement of baseline FVC (% predicted) by ≥ 10 points, no change in pulmonary function when FVC differed from baseline value by < 10 points (% predicted), or decline in baseline FVC (% predicted) by ≥ 10 points. CYC was entered as an independent variable either in a continuous form (cumulative dose in grams) or in a categorical form (0 = not administered, 1 = equal or less than 12 gr, and 2 = higher than 12 gr). Univariate and multivariate analyses were performed and the corresponding odds ratios (ORs) with their 95% confidence intervals (CIs) were calculated. DLCO was not included in the multivariate analysis because of missing values in one sixth of the entire patient cohort. Significance was set at the 0.05 level. The data are presented as mean ± SD. A commercially available statistical software (STATA V8) was used for analysis.

Results

The patients' characteristics are summarized in Table I. Of the 59 patients who met our criteria and included in the study, ILD shown by thoracic CT was present in 57 out of 59 patients. Twenty-nine (49%) patients received IV CYC treatment with the average cumulative CYC dose being 13.9 ± 6.1 (range 5.2-26.2 gr). The average treatment duration was 3.3 ± 2.4 years (range 5-60 months). Ten out of 59 patients (17%) improved their pulmonary function, characterized by at least a 10-point sustained increase in FVC (% predicted) compared to baseline. Eight of these 10 patients received pulse CYC during the course of their disease whereas the remaining 2 patients had spontaneous improvement.

Table I. Clinical and laboratory characteristics of scleroderma patients.

	Scleroderma patients (n = 59)
Gender	
Female	48 (81%)
Male	11 (19%)
Age at disease onset, yrs	47.5 ± 13.9
Total Skin Score	13.8 ± 8.2
Raynaud's phenomenon	59 (100%)
Esophageal involvement	42 (71%)
Renal involvement	0 (0%)
Duration of follow-up, yrs	4.6 ± 2.6
Baseline FVC, % pred	75 ± 20.2
Baseline DLCO, % pred	63.9 ± 25.7
Anti-topoisomerase I, (%)	48 (81%)
Anti- centromere, (%)	5 (8%)
PFT, number	4 ± 1.7
CYC cumulative dose, gr	13.9 ± 6.15
CYC treatment duration, yrs	3.3 ± 2.4
Corticosteroids	
High dose	18 (30.5%)
Low dose	41 (69%)
Decrease in FVC (%)	12/59 (20.3%)
Stable FVC (%)	37/59 (62.7%)
Increase in FVC (%)	10/59 (17%)

Values are given as the mean ± SD or no. (%); CYC: cyclophosphamide; PFT: pulmonary function tests.

In univariate analysis (Table II), CYC was the only variable tested in a continuous or categorical type that was significantly associated with sustained FVC improvement. Specifically, patients treated with CYC were more likely (7% greater likelihood for each CYC gram received) to improve their pulmonary function than develop either pulmonary function decline or no change in pulmonary function. Likewise, after stratification, patients receiving high dose CYC (> 12gr cumulative dose) were 6 times more likely to experience improvement than decrease or maintain the pulmonary function, compared to those who did not receive CYC or those receiving IV CYC less than 12 gr. By contrast, low dose CYC (< 12 gr cumulative dose) was not associated with FVC improvement. The significant effect of high dose therapy persisted (OR 10.82) after adjusting for other covariates in the multivariate analysis (Table III). None of the remaining variables was found to be associated with pulmonary function improvement.

Figure 1 shows the relationship of predicted probabilities of pulmonary function improvement and the cumulative CYC dose (in grams), as derived from the univariate analysis. As shown in Figure 1, increasing cumulative CYC dose was associated with a greater probability of FVC improvement.

The CYC related toxicity included three cases of grade 1 and three cases of grade 2 toxicity. Additionally, two patients experienced panic attacks during CYC infusion and subsequently declined to continue therapy; these two patients had received treatment for a total of 6 and 10 months, respectively. No patient developed renal crisis or overwhelming infection.

Discussion

In a group of patients with SSc and ILD, our data suggest that prolonged (> 1 year) therapy with IV CYC may have a greater probability of pulmonary function improvement than shorter (< 1 year) therapy with CYC.

Interstitial lung disease, a frequent complication in patients with SSc, is usually resistant to treatment and ac-

Table II. Results of univariate analysis showing variables with an independent effect on pulmonary function improvement.

Variable	OR*	95% CIs	*p* value
Baseline DLCO	0.99	0.97 to 1.01	0.56
Baseline FVC	0.99	0.96 to 1.01	0.42
Age at diagnosis	0.99	0.96 to 1.03	0.86
Disease duration	0.99	0.85 to 1.14	0.93
Anti-topoisomerase I	1.22	0.34 to 4.43	0.75
Corticosteroids	2.07	0.64 to 6.74	0.22
CYC cumulative dose, gr	1.07	1.00 to 1.14	0.03
CYC ≤ 12 gr	1.06	0.28 to 4.00	0.92
CYC > 12 gr	6.13	1.53 to 24.4	0.01

*Improve *vs.* stable or worse; CYC: cyclophosphamide.

Table III. Results of multivariate analysis showing variables with an independent effect on pulmonary function improvement.

Variable	OR*	95% CIs	*p* value
Baseline FVC	1.00	0.96 to 1.03	0.98
Age at diagnosis	1.00	0.96 to 1.04	0.98
Disease duration	1.00	0.84 to 1.19	0.94
Anti-topoisomerase I	0.96	0.20 to 4.49	0.96
Corticosteroids	0.50	0.09 to 2.98	0.45
CYC ≤ 12 gr	1.40	0.27 to 7.33	0.69
CYC > 12 gr	10.82	1.41 to 83.03	0.02

*Improve *vs*. stable or worse; CYC: cyclophosphamide.

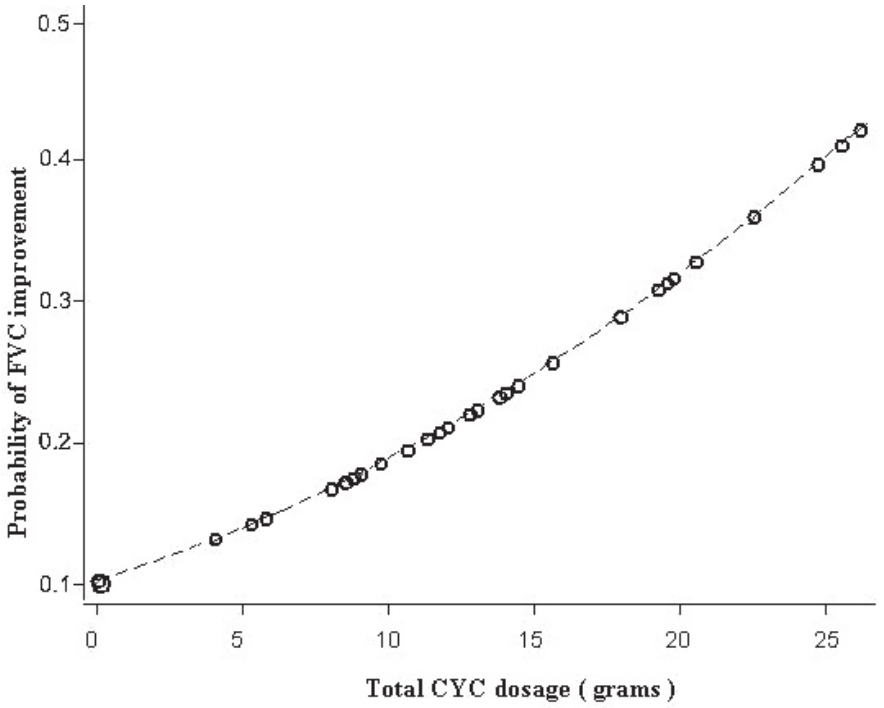

Fig. 1. Relationship of probability of forced vital capacity (FVC) improvement and cumulative cyclophosphamide (CYC) dose in patients with scleroderma and interstitial lung disease. Note that the greater the cumulative CYC dose, the higher the probability of FVC improvement.

counts for a substantial portion of mortality in these patients (2, 5, 13). Of all treatment regimens tested in SSc patients with ILD, only CYC has shown some promise in improving pulmonary function and perhaps survival (16). Several studies, retrospective or uncontrolled, showed improvements of FVC (6, 7, 9, 13, 14, 16, 17, 22), and less frequently of DLCO (6, 9, 11). The average increases in FVC varied significantly among studies, ranging from 2 to 3.5 (% predicted) over a period of 6 to 24 months. These increases in FVC, which are usually detected after treatment for at least 6 months, are not different between patients treated with oral or IV CYC (11, 16). Unlike FVC, DLCO improvements were not consistent among studies (7, 11, 23, 24). Therapy discontinuation is usually accompanied by worsening of pulmonary function (17). In a retrospective study, White *et al*. (16) also showed that treatment with oral CYC improved survival in patients with SSc and ILD.

The efficacy of CYC therapy was recently confirmed by a randomized placebo controlled study in which oral CYC was administered for a year (18). The small improvements of FVC and TLC, but not of DLCO, were also accompanied by improvements of certain clinical parameters such as dyspnea, skin thickening, and functional ability. In the same study (18), pre-existing fibrosis as assessed by the CT score identified a subgroup of patients with relatively early active SSc who were at greater risk for progressive ILD, unless treated.

In the present study, we used strict criteria to define pulmonary function improvement. The threshold of a FVC improvement by at least 10 points (% predicted) is relatively high and greater than the within-individual variation in pulmonary function measurements (16). Furthermore, because only sustained FVC improvements were considered, possible errors related to regression toward the mean were unlikely. When a lower threshold of FVC improvement (5 points, % predicted) was used, the analysis yielded essentially similar results (data not shown).

Steroid dosage (high or low) was not associated with pulmonary function improvement in the present study. In our previous study (13), high doses of prednisolone combined with IV CYC were more efficacious in improving pulmonary function and radiological picture on CT than low prednisolone doses. Differences in methodology and outcome criteria most likely account for the discrepancy between the present and previous study (13). Specifically, in the current study improvement was defined as an increase in FVC (% predicted) by at least 10 points that was required to remain in the same range in all subsequent measurements. In contrast in the previous study (13), differences in FVC (including those that were smaller than 10 points % predicted) were compared between patients receiving low and high dose prednisone. It should be noted that high but not low dosage steroids have been associated with development of renal crises in scleroderma (25, 26). The possible synergistic effects of steroids and CYC on pulmonary function will have to be assessed by controlled studies.

Few studies have used CYC in patients with SSc and ILD for longer than 18 months. Silver *et al*. (14) used oral CYC for about two years and noticed improvements of FVC that were comparable to those found in the present study. In that study (14), 4 out of 11 patients in whom pulmonary function data were available improved the FVC late (*i.e*. after the first year) in the treat-

ment course. However, the total CYC dosage in the study of Silver *et al*. (14) was several times greater than that administered to our patients and was associated with toxicity. In our clinical practice, we initially administered IV CYC for period of about one year. As experience with drug efficacy and adverse effects grew, we extended therapy beyond the conventional period of one year. In the absence of a standardized treatment protocol, the criteria for extending therapy were largely based on patient compliance, and lack of serious toxicity. In agreement with our findings, a recent preliminary study by Dass *et al*. (29) also suggested that long duration of IV CYC therapy (about 2 years) might be associated with greater increase in FVC and be more effective than shorter courses of CYC therapy. Ultimately, the optimal duration of CYC treatment as well as choice of appropriate maintenance therapy (27) post–CYC treatment will have to be determined by controlled randomized studies. In this respect, a recent randomized controlled study showed that treatment with low-dose prednisolone and IV CYC for six months followed by oral azathioprine stabilized lung function in a subset of patients with SSc and ILD (19).

The limitations of the present study should be acknowledged. The study sample was relatively small which in conjunction with the substantial variability in the evolution of pulmonary function reported for SSc patients with ILD (4, 28) makes interpretation of therapeutic trials extremely difficult and conclusions about agent toxicity precarious. The patients who did not receive CYC had essentially normal pulmonary function despite evidence of parenchymal infiltrates on lung CT. Thus, the entire patient group was non homogenous in terms of baseline pulmonary function, which may have introduced a biasing effect on the CYC related improvement. However, because duration of follow up was long, these non treated patients who started off with near normal pulmonary function ended up with a greater decline of pulmonary function than those treated with CYC (-4 ± 11.1 *vs*. 4 ± 14.6 points % predicted FVC for untreated and treated patients, respectively, $p = 0.014$). Finally, there is a possibility of selection bias as only surviving patients or patients who did not drop out due to drug toxicity were likely to be included in the study. However, in our study there were no deaths and the two patients who dropped out after six-month treatment with CYC were also included. The association between treatment duration and pulmonary function improvement found by the present retrospective study warrants confirmation by large prospective studies.

In conclusion, our data suggest that therapy CYC is the only variable independently associated with pulmonary function improvement and that prolonged (> 1 year) CYC therapy may increase the probability of pulmonary function improvement more so than treatment lasting less than a year.

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