Intravenous cyclophosphamide therapy for systemic sclerosis. A single-center experience and review of the literature with pooled analysis of lung function test results

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Abstract

Objective

Oral cyclophosphamide (CYC) is a promising therapy for Systemic Sclerosis (SSc)- related interstitial lung disease (ILD). The use of intravenous (iv) pulses has been considered as an alternative route of drug administration, possibly associated with reduced toxicity. Our objectives were to re-evaluate our experience with iv CYC, to review the literature, and to pool our results with those available from other groups, improving the statistical power of the analysis.

Methods

1) Retrospective analysis of our center experience on 16 patients with SSc and active alveolitis, treated with iv CYC 750 mg + 6-methylprednisolone 125 mg every 3 weeks. 2) Pooled analysis of papers published in peer-reviewed journals reporting detailed data on each patient treated with iv CYC. The end-point was modification in the results of lung function tests (LFT) after 6 months. Piecewise regression analysis was performed using a linear mixed-effects model adjusted for baseline values to evaluate the changes in LFT.

Results

Retrospective analysis. In the period before therapy there was a significant deterioration in FVC (in 6 months: -4.3%; p=0.0009) and DLCO (-2.1%; p=0.018). After 6 months of treatment there was a modest improvement in the FVC (+2.7% p=0.08) and DLCO (+2.2%; p=0.08).

Pooled analysis. In 53 evaluable patients, the improvement in LFT reached conventional statistical signifcance (FVC: +2.85%; 95% confidence intervals: +0.04, +5.66%; p= 0.04. DLCO: +4.4%; 95% confidence intervals: +1.2%, +7.5%; p<0.001).

Conclusion

I*v CYC for 6 months can achieve a small, but significant improvement of LFT in patients with SSc and active alveolitis.*

Key words

Systemic sclerosis, cyclophosphamide, interstitial lung disease.

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Introduction

Interstitial lung disease (ILD) is a frequent manifestation in patients with Systemic Sclerosis (SSc), and one of the leading causes of death (1). No therapy has been demonstrated to be effective for SSc-related ILD in randomised controlled trials, but several uncontrolled studies concordantly showed a significant improvement of forced vital capacity (FVC) in patients treated with daily oral cyclophosphamide (CYC) (2-6). In a retrospective study, this improvement was significantly greater than that observed in patients who received other treatments (D-Penicillamine, prednisone, other immunosuppressive drugs) (4). Another retrospective study suggested that SSc patients with alveolitis who received oral CYC had a better survival than those that were not treated (6).

Due to the substantial toxicity of oral CYC, the use of intravenous (iv) pulses has been considered as an alternative route of drug administration, which may be associated with reduced toxicity. After the reports of very small case series (< 8 patients) (6-9), three larger (14-28 patients) open studies have evaluated this approach (10-12). They showed a "stabilization" of ILD, but failed to demonstrate a significant improvement of lung function tests (LFT), except in a subgroup of patients who also received high-doses of oral glucocorticoids (10). However, the lack of statistical significance of the small changes of the LFT observed in these series might be explained by the small number of patients included, causing a lack of statistical power of these studies and leading to false negative results.

We have re-evaluated our experience with iv CYC in 16 patients and observed results similar to those reported by other authors. In order to better evaluate the effect of iv CYC we have reviewed the literature and pooled our results with those available from other groups, improving the statistical power of the analysis.

Materials and methods

Patients

Between 1995 and 2002, 16 consecutive patients with SSc and active alveolitis were treated with CYC using the same protocol at our Institution. Their main demographic and clinical features are reported in Table I. All patients fulfilled the American Rheumatism Association criteria for classification of SSc (13), and were classified as limited or diffuse SSc (lSSc, and dSSc, respectively) according to the criteria of LeRoy *et al.* (14). Disease duration was defined as time from the onset of first symptom other than Raynaud's phenomenon and patients were classified as having early disease (less than 3 year disease duration for dSSc, or less than 5 year disease duration for lSSc), or late disease. Diagnosis of active SSc-related ILD was based on bronchoalveolar lavage (BAL) findings (n=10), and/or ground glass opacities documented by high resolution computed tomography (HRCT). No patient had clinically relevant pulmonary arterial hypertension (systolic pulmonary artery pressure estimated by echocardiography was < 40 mmHg). In the 6 months preceding the period of CYC treatment, 6 patients received no treatment with immunosuppressive or disease-modifying drugs; one patient was treated with D-Penicillamine, and 9 patients with low-dose oral glucocorticoids (median dosage 10 mg/d; range 5-20), in one case together with D-Penicillamine and in three cases with immunosuppressive drugs (1 Azathioprine; 2 Methotrexate + Cyclosporin).

Cyclophosphamide treatment

All patients received every three weeks iv pulses of CYC 750mg + 6-methylprednisolone 125 mg. In 2 patients the dosage of CYC was reduced to 500 mg every 3 weeks for mild episodes of nausea. No other side effects (leucopenia, infections or haemorrhagic cystitis) were recorded. Fertile women received oral progestinic to block menses and preserve ovarian function. Since 2000, oral mesna was prescribed for the prevention of haemorrhagic cystitis. All patients received also low-doses oral prednisone at a stable dosage (5-20 mg/die), vasodilators (Calcium-channel blockers or Angiotensin Converting Enzyme inhibitors) and platelet inhibitory drugs (low-dose aspirin). Three

patients received cyclic intravenous Iloprost for severe ischemic digital ulcers (15). No patient received other immunosuppressive drugs during the period of the study.

Lung function tests

FVC and diffusion lung capacity for carbon monoxide (DLCO) were evaluated by standard procedures and results were expressed as percentages of predicted values based on age, sex, and height. Normal values were calculated by reference standards provided by the European Coal & Steel community (16, 17).

Review of the literature and pooled analysis

A Medline search was performed using "systemic sclerosis" or "scleroderma", and "cyclophosphamide" as index terms. In the pooled analysis, papers published in peer-reviewed journals were included if they reported detailed data on each patient treated with iv pulses of CYC for ILD in SSc. The indication for this treatment should have been based either on LFT, HRCT or BAL. Patients receiving simultaneously other immunosuppressive drugs or long-term high-doses of oral glucocorticoids were not considered. Low-dose oral glucocorticoids and boluses were allowed. The end-point was a modification of FVC and DLCO (expressed as % of predicted values) after 6 months of treatment. For each study, mean changes and 95% confidence intervals (95% C.I.) were calculated. Between-study heterogeneity was assessed by the Q statistic.

Statistical analysis

Data are presented as the median (25th and 75th percentiles, IQR). Piecewise regression analysis was performed using a linear mixed-effects model adjusted for baseline values to evaluate the changes of LFT during time intervals. The statistical package R was used to perform the statistical analysis.

Results

Retrospective analysis of our centre experience

Eleven of the 16 patients with SSc who received iv CYC for ILD performed at least two LFT before the start of therapy. Considering the first and the last tests before treatment with CYC, the median interval was of 11 months (IQR: 5, 30). During this interval, a significant deterioration of FVC and DLCO was observed (Fig. 1, data standardized at 6 months are shown). There was no difference between patients that, during this period, received immunosuppressive drugs (n=3) or not, or low-dose oral glucocorticoids (n=7) or not (data not shown). After 6 months of therapy with iv CYC, the slope was significantly changed from the previous interval ($p<0.05$). As shown in Figure 1, there was a modest increase from baseline of FVC and DLCO. However, this did not reach conventional statistical significance. These results were not different when patients were separated according the treatment received in the period preceding the use of iv CYC (data not shown).

Table I. Main demographic, clinical and laboratory characteristic in 16 patients treated with iv CYC for ILD due to SSc. Data are presented as the median (25th and 75th percentiles).

Characteristic		
Sex (M/F)	1/15	
Age (years)	49.5	(42.75, 57.5)
Disease subset (dSSc/lSSc)	9/7	
Disease duration (months)	28.5	(17.5, 75.25)
Anti-Scl70	7	(44%)
Oral prednisone dose	10	(7, 15)
FVC, % predicted	83	(71, 98.75)
DLCO, % predicted	46	(39.5, 51.25)
BAL(n=10), total cells	310,000	(265,000, 530,000)
BAL(n=10), % neutrophils	10	(8.4, 19.5)

Review of the literature and pooled analysis

Table II summarizes the patient characteristics, treatment protocols and results from other studies reporting the effects of iv CYC for SSc-related ILD. The two studies, which have enrolled the highest number of individuals treated in this way, without high-doses of oral glucocorticoids, reported detailed results on each patient (11, 12). In these two studies the protocols of treatment were similar to our protocol, as far as the dose of iv CYC used. A pooled

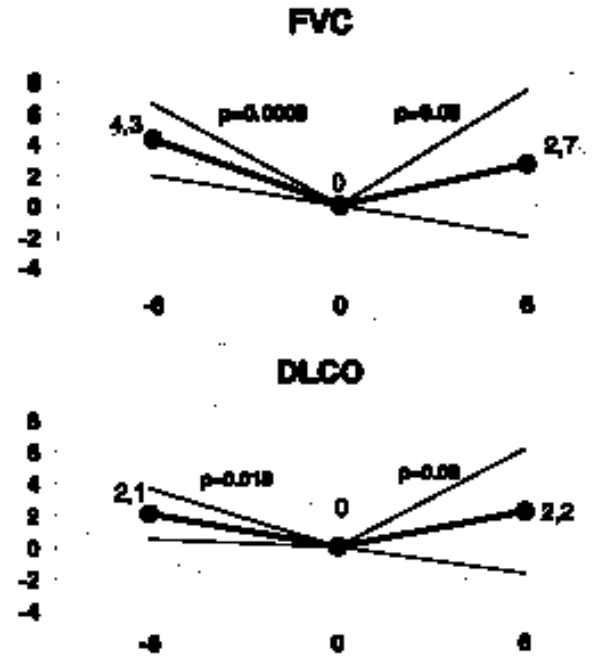

Fig. 1. Changes in Forced Vital Capacity (FVC) and Diffusion Lung Capacity for CO (DLCO) before and after therapy with iv CYC. The mean and 95% confidence intervals values are indicated, considering data at the initiation of therapy = 0. Data before the treatment were standardized at 6 months.

Table II. Patient characteristics, treatment protocols, and efficacy of iv CYC therapy for ILD due to SSc reported in the literature.

Reference	Varai (8)	Davas (9)	Pakas (10)*	Griffiths (11)	Giacomelli (12)	This study
Patients, no.	5	8	12	14	23	16
dSSc/lSSc	2/3	8/0	8/4	NR	17/6	9/7
Disease duration (mo.)	26	NR	58	24	NR	28.5
CYC dosage	1 g/mo.	750 mg/m^2/mo.	750 mg/m^2/mo.	15 mg/kg/3w then tapered	1 g/m^2/mo.	750 mg/3wk
MPbolus	no	no	no	10 mg/kg	no	125 mg
Oral prednisone	no	10 mg	< 10 mg	no**	25 mg, tapered to 5	5-20 mg
FVC %						
Median pre-CYC	NR	86.1	54.8	92.5	91	83
Median post-CYC	NR	88	NR	98	91	91.5
Mean change	+7 §	NR, p=NS	+ 3.4	+ 2.1	+ 3.4	+ 2.7
(95% C.I.)	NR	NR	NE	-3.4, +7.6	-1.2, +8.0	-1.4, +6.8
DLCO%						
Median pre-CYC	NR	60	38.2	65	50.5	46
Median post-CYC	NR	65	NR	59	64.5	46.5
Mean change	-12 §	NR, p=0.018	+ 2.4	- 2.9	+ 9.3	+ 2.2
(95% C.I.)	NR	NR	NE	-9.2, +3.4	+5.0, +13.7	-1.8, +6.2

NR: not reported; CYC: cyclophosphamide; MP: methylprednisolone; NE: not evaluable; NS: not significant.
* Only data on patients treated with iv CYC and low dose steroids; Pakas *et al*. (10) also treated 16 patients with iv CYC and high doses of oral glucocrticoids.
** 6/14 patients also received low-dose oral prednisolone, with progressive tapering. Further details on these patients were not reported (12).
§ Data at 48 weeks are reported.
Other papers on iv CYC: White *et al*. (6) treated 4 patients with 0.8 - 1.4 g/mo. They are reported together with 35 patients receiving oral CYC. Schnabel *et al*. (7) treated 2 patients with 0.5 g/m^2/mo. Data on LFTare reported together with those of other 4 patients with ILD due to other connective tissue diseases.

analysis was therefore performed, evaluating data from these studies together with ours, for a total of 53 patients. As shown in Figure 2, the obtained results in the overall population were very similar to those observed in our centre in terms of the magnitude of the effect, demonstrating a modest improvement both of DLCO and FVC after 6 months of treatment. However, for the increased power of the analysis, this reached conventional statistical significance (FVC: +2.85%; 95% C.I.: +0.04, +5.66%; p=0.04. DLCO:+4.4%; 95%C.I. +1.2%, +7.5%; p<0.001). Between study heterogeneity was analysed by analysis of variance. While there was no effect of the center provenience on the FVC results, patients from the study of Giacomelli *et al.* (12) had significantly better DLCO results than patients from the study of Griffiths *et al*. (11) and than our patients (p = 0.03).

A specific analysis was also performed, evaluating the hypothesis of a different effect of CYC treatment on patients with early or late disease. Patients from the study by Griffiths *et al.* (11), and from our institution could be evaluated in this way; no difference between groups of patients divided according to this parameter was observed.

Adverse events

Among the 53 patients treated with iv CYC evaluated at our institution, or in the two studies considered in the pooled analysis of efficacy, no cases of se-

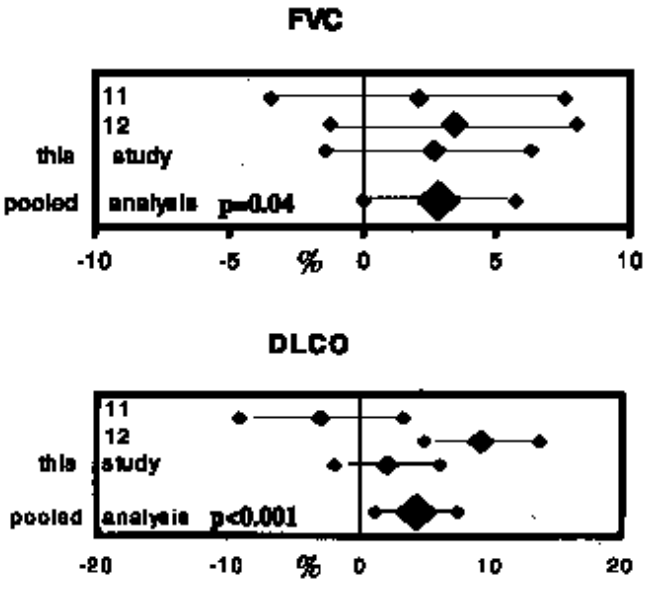

Fig. 2. Changes in Forced Vital Capacity (FVC) and Diffusion Lung Capacity for CO (DLCO) after 6 months of therapy with iv CYC in each of the three studies considered in the pooled analysis and in their sum. The mean and 95% confidence intervals values are indicated. Symbols are proportional to the number of patients included in the studies.

vere infections or haemorrhagic cystitis were reported, while 1 patient suffered from leucopenia (11). The rate of severe adverse events over 6 months was therefore 1.9% (95% C.I.: 0.04-10.1).

Discussion

In patients with SSc, ILD results from alveolitis, which lead to interstitial fibrosis (1). Due to their feasibility and reliability, LFT have been included in the core set of variables reflecting the occurrence of SSc-related ILD (18). Moreover, they have been proven to be highly significant prognostic factors in determining the progression of lung disease and survival of patients with SSc (1, 19, 20). Several studies showed that in untreated patients there is a progressive decrease in FVC and DLCO (1).

In the present study, 16 patients with a relatively short disease duration showed a statistically significant deterioration of FVC and DLCO and active alveolitis as determined by BAL and/or HRCT. After treatment with iv CYC these patients experienced a small improvement in their LFT. These findings were very similar to those concordantly observed in the short-term by others (8-12), who demonstrated an analogous small improvement in patients treated with iv CYC (and variable doses of glucocorticoids). However, in our series as in other single centre studies, this improvement was not statistically significant due to the small numbers of patients evaluated.

Meta-analysis is an approach that – by combining appropriately the results of relevant studies – may allow one to arrive at conclusions regarding a body of research. Although it is generally applied to randomised controlled trials, a growing number of meta-analyses of observational studies has appeared in the literature (21). We considered therefore that a pooled analysis of studies on iv CYC in SSc-related ILD could answer to the question as to whether the observed small improvements were fortuitous or not. We evaluated together data from our centre and from other two studies (11, 12), that had only minor differences in the treatment protocols as far as the use of iv CYC was concerned, and that reported detailed data on each patient. These three series are the largest available in the literature in which the effect of iv CYC could be evaluated without the effect of a high dose of oral glucocorticoids. The results of this pooled analysis suggest that the improvement in LFT after iv CYC, although small, is not random. This is particularly interesting since in these series the disease duration was rather short, and it has been suggested that the progression of ILD is more rapid in the first years of disease (22). However, it should be noted that we did not observe any difference in the response to iv CYC in patients with early disease compared with those with late disease.

Possible biases that may have influenced our observation of an improvement of LFT after iv CYC are: publication bias and regression-to-the-mean bias. The lack of publication of unfavourable results cannot be excluded; however, given the great interest and scarcity of information on this approach and the lack of alternative treatments of proven efficacy, this is unlikely. It should be noted that most authors of previous studies were very cautious in the interpretation of their results.

As suggested (10), regression-to-the-mean bias may also influence the interpretation of studies in which low LFT were an eligibility criterion. However, regression-to-the-mean may explain improvements in the indices by which patients were selected, but not changes in other outcomes. Of note, the other authors included in the meta-analysis (11, 12) and we treated patients on the basis of HRCT and/or BAL findings and not on those of LFT, thus suggesting that regression-to-the-mean was not an important factor in determining the results observed in the pooled analysis.

A limitation of our analysis was that it was focused only on LFT results and did not consider other markers of ILD, such as HRCT and BAL scores. This limitation was due to the fact that our patients did not repeat the HRCT or BAL after 6 months. This policy was chosen to avoid the repetition of costly and invasive procedures; moreover, the clinical relevance of variations in HRCT and BAL parameters after such a short interval is less defined than that of variations in LFT. Pooled analysis of literature data is made difficult by the scarcity of data on repeated BAL analyses and by the fact that in different studies evaluating modifications in HRCT, different scoring systems were used.

Nevertheless, based on the available data there is a fairly consistent pattern of positive effects of iv CYC therapy in SSc, also on HRCT and BAL findings. In fact, it has been reported that this treatment induced regression of areas of ground glass opacities on HRCT(9), particularly in patients with very early lung disease (11), although sometimes this regression was not statistically significant (12). In another study, this result was observed only in a subgroup of patients who also received high-dose oral glucocorticoids (10). However, patients receiving CYC + low-dose oral steroids in this study had particularly long and severe disease (see Table II). An improvement of the BAL findings, with a reduction in the total cell number and lymphocyte percentage was reported by Varay *et al.* (8); a reduction, although not statistically significant, was also observed in the only other study which evaluated repeated BAL tests (12). It should be recalled that the small number of patients involved in single-center studies might limit the probability of detecting moderate but statistically significant improvements in the HCRT and BAL findings. Taken together, these observations suggest that iv CYC might have a favourable effect on ILD parameters other than LFT, thus supporting the hypothesis arising from our pooled analysis that iv CYC for 6 months can induce a significant improvement of LFT in patients with SSc and active alveolitis.

However, it should be underlined that this improvement is small and that more data are needed to ensure that it is also clinically relevant. The role of glucocorticoids and the optimal dosage of CYC are also undetermined. Regarding the use of glucocorticoids, Pakas *et al.* compared patients receiving iv CYC

plus either low or high doses of oral prednisolone (10). Significant improvements in the LFTand HCRTscores were noted only in the high dose steroid group. These results suggest a role for high-dose steroid in the treatment of SSc-related ILD. However, the two groups were not randomized and patients in the low-dose group had longer and more severe ILD than other patients. Thus, the authors could not conclude that the two regimens had different efficacies (10). In our pooled analysis, between-study heterogeneity analysis disclosed that in the study of Giacomelli *et al.* (12), the effect on DLCO results was better than those observed in the other studies. It is unclear whether this observation was related to the use of oral glucocorticoids by these authors at a dosage that was initially higher than those used by us and by Griffiths *et al.* (11), who in fact did not use oral glucocorticoids in most patients (see Table II). To further complicate the interpretation of the data, it should be noted that on the contrary Giacomelli *et al.* did not use 6-methylprednisolone boluses whereas these were administered, albeit at different dosages, to patients in our centre and in the study of Griffiths *et al.* (Table II). Moreover, no difference between studies was found as far as the results of iv CYC on FVC, i.e. the parameter related to restrictive lung disease, are concerned: in all studies a very similar improvement in this index was observed.

On the other hand, Giacomelli *et al.* used slightly higher doses of CYC than the other authors, and this could also be relevant. Another unresolved issue, as far as the optimal use of CYC is concerned, is its duration: the longer term follow-up data of patients treated with CYC for 6 months suggests that deterioration after stoppage of treatment occurs in most patients, sometimes at a significant rate (11), while in patients prolonging the treatment for 12 months, Davas *et al.* observed further improvement (9). This was also found by Pakas *et al.* in the group receiving CYC plus high-dose steroids (10). It is therefore likely that treatment with iv CYC should be prolonged beyond six months, but the best schedule remains to be determined.

Finally, in agreement with previous reports (8-10), the pooled analysis of the three studies showed that treatment with iv CYC was very well tolerated: only 1 patient out of 53 experienced leukopenia, and no cases of severe infection or haemorrhagic cystitis were reported. The long-term adverse events of CYC including infertility, cumulative bone marrow toxicity, and carcinoginesis, are dose-dependant and therefore would be expected to be less frequent and severe using iv rather than oral CYC protocols.

Our findings clearly indicate that prospective, multi-center, randomised controlled trials are needed to appropriately evaluate the utility of this treatment in SSc-related ILD.

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