Arch Bronconeumol. 2011;**47(5)**:239-245

ARCHIVOS DE BRONCONEUMOLOGIA

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Original Article

Efficacy of Cyclophosphamide in the Treatment of Interstitial Lung Disease Associated with Systemic Sclerosis

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ARTICLE INFO

Article history:
Received October 5, 2010
Accepted January 13, 2011

Keywords:
Interstitial lung disease
Systemic sclerosis
Cyclophosphamide
Treatment

ABSTRACT

Background: Cyclophosphamide (CYC) stabilizes the parameters of lung function tests (LFT) of patients with systemic sclerosis (SSc) and interstitial lung disease (ILD) treated for 12 months. There is little information about long-term treatment (24 months). The aim of this study is to analyze the effect of intravenous CYC in LFT parameters in patients with SSc and ILD treated for 24 months.
Patients and method: Retrospective study of 37 patients with ILD associated with scleroderma treated with intravenous CYC for 24 months and regularly assessed by LFT (at baseline, 6, 12 and 24 months) including forced vital capacity (FVC) and transfer capacity of carbon monoxide (DL_{CO}).
Results: The differences between FVC and DL_{CO} values performed at baseline and those performed at 6, 12, and 24 months were less than 10%, which meant that CYC stabilized functional parameters. There were no differences in FVC or DL_{CO} when patients treated for 6 months were evaluated according to the type of SSc skin involvement of (diffuse or limited) or according to the evolution time of ILD before the start of treatment. Although patients with severe restriction (FVC<70%) showed more improvement, it was less than 10% in all cases.
Conclusion: In this series of patients with ILD associated with SSc, intravenous CYC was effective in stabilizing lung function parameters in long-term treatment.

Eficacia de la ciclofosfamida endovenosa en el tratamiento de la enfermedad pulmonar intersticial asociada a la esclerosis sistémica

Palabras clave:
Enfermedad pulmonar intersticial
Esclerosis sistémica
Ciclofosfamida
Tratamiento

RESUMEN

Introducción: La ciclofosfamida (CFM) estabiliza los parámetros del estudio funcional respiratorio (EFR) de los pacientes con esclerosis sistémica (ES) y enfermedad pulmonar intersticial (EPI) tratados durante 12 meses. Existe poca información acerca del tratamiento a largo plazo (24 meses). El objetivo del estudio es analizar el efecto de la CFM endovenosa en los parámetros del EFR de los pacientes con ES y EPI tratados durante 24 meses.
Pacientes y método: Estudio retrospectivo de 37 pacientes con EPI asociada a esclerodermia, tratados con CFM endovenosa durante 24 meses y evaluados de forma periódica mediante EFR (basal, a los 6, 12 y 24 meses). En este se evaluó la capacidad vital forzada (FVC) y la capacidad de transferencia de monóxido de carbono (DL_{CO}).

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0300-2896/$ - see front matter

Resultados: Las diferencias entre los valores de FVC y DL_{CO} basales y los realizados a los 6, 12 y 24 meses fueron menores del 10%, lo que significa que la CFM estabilizó los parámetros funcionales. Tampoco se detectaron diferencias en la FVC ni en la DL_{CO} cuando se valoró a los pacientes tratados durante 6 meses de acuerdo al tipo de afectación cutánea de la ES (difusa o limitada), o según el tiempo de evolución de la EPI antes del inicio del tratamiento. Si bien los pacientes con restricción grave (FVC < 70%) al inicio mostraron mayor mejoría, esta fue en todos los casos inferior al 10%.
Conclusión: En esta serie de pacientes con EPI asociada a ES, la CFM endovenosa estabilizó los parámetros funcionales respiratorios en el tratamiento a largo plazo.

1. Introduction

Systemic sclerosis (SSc) is a disease characterized by the coexistence of an autoimmune base, a microvascular affectation and an increase in the production and deposits of collagen in the skin (scleroderma) and in different organs (lungs, digestive tract, heart and kidneys).[1] The two most important pulmonary manifestations are interstitial lung disease (ILD) and pulmonary artery hypertension (PAH),[2] which are the main causes of death in these patients.[3] Specifically, about 16% of these deaths are directly due to ILD.[2]

ILD is more frequent in patients with diffuse skin affectation. The most characteristic anatomopathologic lesion, present in more than 75% of patients, is non-specific interstitial pneumonia.[4] The physiopathological mechanism of ILD in SSc is not exactly understood, but it includes immunological and inflammatory processes as well as vascular damage. It has been proposed that the collagen deposits are produced by the interactions between the endothelial cells, mononuclear cells (lymphocytes and monocytes) and fibroblasts. All this would trigger the production of fibrosis activating cytokines in the context of vascular hyperreactivity and tissue hypoxia.[5]

Lung function tests (LFT) play a key role in the diagnosis of ILD in patients with SSc. It is a mildly invasive procedure that is easy to perform, useful for evaluating the existence, intensity and progression of ILD in these patients.[6] LFT should include arterial blood gas, spirometry (FVC) and diffusing lung capacity for carbon monoxide (DL_{CO}). A restrictive pattern with reduction of FVC and normal FEV1/FVC ratio is most frequent.

Currently, the most realistic objective in treating ILD associated with SSc is to avoid ILD progression, especially in those patients with a more extensive affectation of the pulmonary parenchyma.[7] The immunosuppressant that is most frequently used is cyclophosphamide (CYC). The results of three prospective randomized controlled studies, with FVC and DL_{CO} as variables being studied, suggested that CYC treatment, both oral[8,9] as well as intravenous[10] for 12 months, can stabilize ILD in patients with SSc. A meta-analysis that compiled the results of these studies and 6 observational studies confirmed this finding, with a low incidence of secondary effects with the use of said drug.[11] In addition, some studies in which treatment with CYC was administered for only 6 months have also demonstrated effectiveness.[12,13] Therefore, the use of CYC is currently recommended for the treatment of ILD in patients with SSc.[14,15]

The majority of the studies included in the meta-analysis evaluated the effect of the immunosuppressant treatment after 12 months and in only two of them the follow ups were 18[16] and 24[17] months, respectively.

The objective of this present study is to analyze retrospectively, using FVC and DL_{CO} serial measurements, the short-term (6 months), mid-term (12 months) and long-term (24 months) effects of treatment with intravenous pulses of CYC on the evolution of ILD in a cohort of patients with SSc.

2. Patients and Methods

2.1. Patients

We have carried out a retrospective analysis of all the patients with SSc and ILD who had undergone treatment with intravenous pulses of CYC in the Autoimmune Disease Department at the Hospital Clinic (HCB) and in the Internal Medicine Department at the Hospital Vall d'Hebron (HVH) in Barcelona during the period between December 1996 and February 2007. Excluded from the study were those patients who presented other lung lesions and those who could not be controlled during follow-up. All of the patients included were affected by SSc according to the accepted classificatory criteria.[18] The presence of associated ILD was confirmed when given compatible symptoms and/or the existence of a restrictive pattern in the LFT and findings compatible with ILD on thoracic high-resolution computed tompgraphy.[19] In those cases that caused doubt, other diagnoses, such as infection or neoplasia, were ruled out by means of the corresponding complementary explorations. In addition, the coexistence of PAH was ruled out by ultrasound and right catheterization in those cases in which this was indicated.

We collected other epidemiological and clinical data that were not included in the objectives of the disease, such as age, sex, type of scleroderma and the degree of dyspnea according to the classification of the *New York Heart Association* (NYHA),[20] prior to the start of treatment. The project was approved by the ethics committees of the two hospitals participating in the study.

2.2. Treatment Algorithms

Treatment consisted of intravenous CYC pulses after pre-established hydration. In the case of the patients treated in HVH, the dose of CYC was 600 mg/m^2 monthly during the first 6 months, bimonthly up to 12 months, and quarterly up to 24 months. The guideline used by the HCB was 750 mg/m^2 body surface; the first 6 pulses were administered monthly, followed by a quarterly regime up to 24 months of treatment. In all cases, this was associated with glucocorticoids in decreasing doses. For the patients treated in the HVH, the initial dose of prednisone was 50 mg/day, which was reduced by 5 mg/week until a dose of 5-7.5 mg/day was reached, which was maintained during the remainder of the treatment. For the patients treated in the HCB, the initial dose was 1 mg/ kg/ day with a maximum dose of 60 mg/day, which was reduced by 10 mg/ month until reaching a dose of 5 mg/day, which was maintained until 2 years of treatment. All the patients received treatment with

calcium supplements and vitamin D in order to prevent osteoporosis induced by glucocorticoids.

2.3. Lung Function Tests

The LFT were carried out in the period between October 1996 and September 2008. All patients underwent determinations of forced spirometry, lung volumes by plethysmography and DL_{CO}. The results were expressed in a percentage compared with that predicted for each patient. Depending on the FVC and DL_{CO} values, the severity of ILD was classified as mild (70-79%), moderate (50-69%) and severe (< 50% predicted values).[21] In order to evaluate the response to treatment by means of LFT values, the recommendations of the *American Thoracic Society* (ATS) and the Spanish Society of Pneumology and Thoracic Surgery (SEPAR)[22,23] were followed. According to these recommendations, an improvement is considered an increase in FVC ≥ 10% or in DL_{CO} ≥ 15%, stabilization if the changes in FVC are less than 10% or 15% in DL_{CO} and worse if there was a reduction in FVC ≥ 10% or DL_{CO} ≥ 15%. In all the patients, LFT were carried out before treatment was started (at the moment of the ILD diagnosis) and repeated at 6, 12 and 24 months from the start of treatment (the latter coincided with the CYC pulse session).

2.4. Statistical Analysis

For the statistical analysis of the comparison of the LFT parameters at the start of treatment and at months 6, 12 and 24, we selected the patients that at each time point had completed the treatment and had undergone the corresponding LFT. For the comparison of categorical variables among the different groups, Fisher's exact test was used. The McNemar test (for two groups) and Cochran's Q test (more than two groups) were used for the comparison of intergroup variables. For continuous variables with 2 groups, Student's t test was used, while ANOVA was used for more than 2 groups.

3. Results

3.1. General Characteristics

Thirty-seven patients were included in the study (21 in HCB and 16 in HVH), whose general characteristics are shown in table 1. All the patients received at least 6 monthly pulses of CYC, 32 (86%) completed the one-year treatment and 26 (70%) patients received treatment for 2 years.

Out of the 21 patients treated at HCB, 12 (57%) completed two years of treatment while 19 (91%) completed one year of treatment as indicated by the specialist in charge. The two remaining patients only received 6 monthly pulses of CYC. One of the patients preferred to continue with the maintenance treatment with mycophenolic acid, and in the other case it was decided not to continue with the immunosuppressant treatment due to the patient's advanced age. Out of the 16 patients treated at HVH, 11 (69%) completed the 2-year treatment. Thirteen (81%) completed the bi-monthly treatment up to one year. The causes for suspension were in one case due to lymphopenia, hypogammaglobulinemia and repeated respiratory infections, and in another due to change of residence of the patient. The 3 (19%) remaining patients completed the treatment with only 6 monthly pulses due to FVC results higher than 80% in the LFT, death by respiratory insufficiency secondary to PAH and the development of lymphopenia, respectively.

There were no differences in the distribution by sexes, type of SSc or distribution of antibodies between the patients depending on the hospital of origin (table 1). It should be noted that the patients treated at HCB presented shorter evolution times of their SSc (38.6 ± 54.8 months vs 91.0 ± 62.1 months; p = 0.011) at the time of the ILD diagnosis. Furthermore, they also presented a shorter evolution time of their ILD at the start of treatment (12.7 ± 17.6 months vs 38.8 ± 41.4 months; p = 0.015). As for dyspnea, at the beginning of treatment 10 (27%) patients presented class III dyspnea, 15 (41%) class II and 12 (32%) functional class I.

Six patients presented PAH when treatment was initiated with CYC, although the mean pulmonary artery pressure levels were less than 35 mm Hg.

The mean dose of glucocorticoids at the start of treatment was 52.1 ± 18.9 mg/ day, at 6 months 13.3 ± 10.3 mg/ day, at 12 months 8.3 ± 4.6 mg/day and at 24 months 7.2 ± 4.4 mg/ day, respectively, with no differences between the two hospitals. The accumulated dose of CYC in the overall total of the series was 10.1 ± 3.7 g, with no differences between the two hospitals.

3.2. Lung Function Tests

In the overall series, the patients presented moderate-mild ILD with FVC and DL_{CO} at 64.9% ± 17.4% and 69.1% ± 17.1%, respectively. As mentioned in the statistical analysis section, in order to evaluate the response to treatment we selected the patients who, at each time point (6, 12 and 24 months) had received treatment and who had completed the corresponding LFT. With this premise, 31 (84%) patients completed the 6 months of treatment with later LFT, 21 (57%) completed the year of treatment with the corresponding LFT and 17 (46%) patients received treatment for two years with LFT at the end of this period. In the overall series, the LFT corresponding with 6 months of treatment was done at 6.1 ± 1.6 months, that corresponding with one year at 13.6 ± 3.6 months and that with two years at 23.6 ± 4.4 months, with no differences detected between the two hospitals.

The determinations of FVC and DL_{CO} in the different time periods are reflected in [Table 2] and [Table 3]. In the global series, there were no significant differences in any of the functional parameters in the different time periods (6, 12 and 24 months). In fact, the differences between the FVC and DL_{CO} at the start and at the end of each treatment were less than 5% in all the determinations.

In the patients treated for 6 months, a significant difference was detected both in the FVC as well as DL_{CO} depending on the hospital of origin (FVC: −2.0% for the patients from HCB versus 3.0% for those from HVH; p = 0.001 and DL_{CO}: −0.9% for patients from HCB versus 2.7% for those from HVH; p = 0.032) (table 2). In the patients treated for 12 months, there were no differences between the two hospitals (table 3). Last of all, in those treated for 24 months, a significant difference was detected in FVC (−2.7% in the patients from HCB versus 3.5% in those from HVH; p = 0.019) and in DL_{CO} (0.4% in those patients from HCB versus −6.1% for those from HVH; p = 0.048) (table 4). However, as indicated, the final values for each functional parameter in the different time periods were similar.

With the intention of evaluating the response to treatment according to the initial severity of ILD measured by FVC, the patients were divided into two groups: with severe restriction before initiating treatment (FVC < 70%) and those with a moderate or mild restriction (FVC ≥ 70%). This range was chosen in following the prospective study by Tashkin et al.[9] The patients with FVC < 70% at the beginning of treatment experienced a significant improvement over those with FVC ≥ 70% in patients treated for 6, 12 as well as 24 months (table 5). In fact, in the patients with mild or moderate restriction there is a tendency towards worsening in the three time periods evaluated. In

Table 1
Demographic, clinical and immunological characteristics of the patients with systemic sclerosis and associated interstitial lung disease

	HCB (n = 21)	HVH (n = 16)	Total series (n = 37)	p[a]
Females	15 (71%)	15 (94%)	30 (81%)	NS
Smokers	6 (29%)	0	6 (16%)	NS
Age at ILD diagnosis (yrs)	43.1 ± 13.3	42.8 ± 13.3	43.0 ± 12.4	NS
SSc evolution time (months)	38.6 ± 54.8	91.0 ± 62.1	61.3 ± 62.9	0.011
Type of SSc				
Diffuse	12 (57%)	10 (62%)	22 (59%)	NS
Limited	6 (29%)	6 (38%)	12 (32%)	
Overlap syndrome	3 (14%)	0	3 (8%)	
ILD evolution time (months)	12.7 ± 17.6	38.8 ± 41.4	24.4 ± 32.8	0.015
Starting functional class (NYHA)				
Class I	5 (24%)	7 (44%)	12 (32%)	NS
Class II	11 (52%)	4 (25%)	15 (41%)	
Class III	5 (24%)	5 (31%)	10 (27%)	
Pulmonary arterial hypertension	4 (19%)	2 (13%)	6 (16%)	NS
ANA	21 (100%)	16 (100%)	37 (100%)	NS
Anti-Scl70 antibodies	7 (30%)	10 (63%)	17 (46%)	NS
Anti-centromere antibodies	2 (9%)	1 (6%)	3 (8%)	NS
FVC at ILD diagnosis (%)	68.3 ± 16.3	60.6 ± 18.4	64.9 ± 17.4	NS
DL_{co} at ILD diagnosis (%)	68.1 ± 17.1	70.7 ± 17.5	69.1 ± 17.1	NS

The continuous variables are presented as mean ± standard deviation. The categorical variables are presented as absolute number and the percentage in parenthesis.

[a]Refers to the comparison between the patients according to hospital. DL_{co}: diffusing capacity of CO; FVC: forced vital capacity; HCB: Hospital Clinic de Barcelona; HVH: Hospital de Vall d'Hebrón; ILD: interstitial lung disease; NS: not significant; NYHA: *New York Heart Association;* SSc: systemic sclerosis.

Table 2
Baseline respiratory functional study and at 6 months of the patients with SSc and ILD treated with monthly pulses of cyclophosphamide for 6 months

Hospital of origin	LFT	At the start of treatment	At 6 months	Difference*
HCB (19)	FVC (%)	70.2 ± 16.3	68.2 ± 16.8	−2.0 ± 3.8[†]
HVH (12)		61.1 ± 14.1	64.1 ± 12.6	3.0 ± 3.9
Global (31)		66.5 ± 15.8	66.6 ± 15.2	0.1 ± 2.8
HCB (19)	DL_{co} (%)	68.7 ± 17.7	67.8 ± 15.6	−0.9 ± 3.8[‡]
HVH (12)		69.6 ± 18.8	72.3 ± 16.1	2.7 ± 5.1
Global (31)		69.0 ± 17.8	69.5 ± 15.6	0.5 ± 3.0

The continuous variables are presented as mean ± standard deviation. The numbers in parenthesis indicate the patients analyzed in each group.

*A positive difference means improvement over baseline; a negative difference means poorer than baseline.

[†]p = 0.001 between the difference of FVC between initial LFT and at 6 months of the patients according to the hospital of origin; [‡]p = 0.032 between the difference of DL_{co} between the initial LFT and at 6 months of the patients according to the hospital of origin; DL_{co}: CO diffusing capacity; FVC: forced vital capacity HCB: Hospital Clinic de Barcelona; HVH: Hospital Vall d'Hebron; ILD: interstitial lung disease; LFT: lung function tests; SSc: systemic sclerosis.

Table 3
Baseline pulmonary function study, repeated at 6 and at 12 months, of the patients with SSc and ILD treated with monthly pulses of cyclophosphamide for one year

Hospital of origin	LFT	At the start of treatment	At 6 months	At 12 months	Difference[a]
HCB (13)	FVC (%)	64.5 ± 16.6	63.1 ± 17.6	65.9 ± 18.4	1.4 ± 4.9
HVH (8)		62.4 ± 12.5	65.6 ± 9.7	63.2 ± 8.1	0.8 ± 3.7
Global (21)		63.7 ± 14.8	64.1 ± 14.7	64.9 ± 15.1	1.2 ± 3.3
HCB (13)	DL_{co} (%)	67.1 ± 20.6	65.1 ± 18.9	68.7 ± 18.7	1.6 ± 5.5
HVH (8)		71.5 ± 20.1	76.9 ± 17.7	70.9 ± 14.7	−0.6 ± 6.2
Global (21)		68.9 ± 19.9	69.4 ± 18.8	69.5 ± 16.9	0.6 ± 4.0

The continuous variables are presented as mean ± standard deviation. The numbers in parenthesis indicate the patients analyzed in each group.

[a]A positive difference means an improvement over baseline; a negative difference means poorer than baseline. DL_{co}: diffusion lung capacity for CO; FVC: forced vital capacity; HCB: Hospital Clinic de Barcelona; HVH: Hospital Vall d'Hebron; ILD: interstitial lung disease; LFT: lung function tests; SSc: systemic sclerosis.

Table 4
Baseline pulmonary function test at 6, 12 and 24 months of the patients with SSc and ILD treated with monthly pulses of cyclophosphamide for two years

Hospital of origin	LFT	At the start of treatment	After 6 months	After 12 months	After 24 months	Difference*
HCB (10)	FVC (%)	67.7 ± 15.9	63.5 ± 15.4	55.8 ± 13.1	65.0 ± 18.6	−2.7 ± 5.5[†]
HVH (7)		59.1 ± 9.2	67.1 ± 9.4	63.9 ± 8.4	62.6 ± 9.5	3.5 ± 3.5
Global (17)		63.9 ± 13.8	65.0 ± 13.0	60.2 ± 11.2	64.0 ± 15.2	0.1 ± 3.5
HCB (10)	DL_{co} (%)	64.6 ± 14.7	65.9 ± 11.3	65.3 ± 19.6	65.0 ± 18.6	0.4 ± 5.3[‡]
HVH (7)		75.7 ± 18.0	76.7 ± 19.4	67.7 ± 12.6	69.6 ± 20.2	−6.1 ± 7.2
Global (17)		69.4 ± 16.7	69.9 ± 15.2	66.6 ± 15.5	64.6 ± 17.1	−4.8 ± 4.1

The continuous variables are presented as mean ± standard deviation. The numbers in parenthesis indicate the patients analyzed in each group.

*A positive difference means an improvement over baseline; a negative difference means poorer than baseline. [†]p = 0.019 between the difference of FVC between initial LFT and after 24 months of the patients by hospital of origin; [‡]p = 0.048 between the difference of DL_{co} between initial LFT and after 6 months of the patients by hospital of origin; DL_{co}: CO diffusing capacity; FVC: forced vital capacity; HCB: Hospital Clinic de Barcelona; HVH: Hospital Vall d'Hebron; ILD: interstitial lung disease; LFT: lung function test; SSc: systemic sclerosis.

Table 5
Baseline pulmonary function test, repeated at 6, 12 and 24 months of the patients treated with 6, 12 and 24 monthly pulses of cyclophosphamide according to the severity of the ILD affectation measured by FVC

	At the start of treatment	After 6 months	After 12 months	After 24 months	Difference*
FVC < 70% (19)	55.4 ± 8.5	59.4 ± 13.0	–	–	4.0 ± 3.6†
FVC ≥ 70% (12)	83.7 ± 9.7	77.2 ± 14.3	–	–	−6.5 ± 4.9
FVC < 70% (15)	53.6 ± 7.9	–	59.1 ± 14.2	–	5.5 ± 4.2†
FVC ≥ 70% (6)	83.0 ± 10.3	–	74.8 ± 17.6	-	−8.2 ± 8.3
FVC < 70% (13)	55.7 ± 9.1	–	–	58.2 ± 13.6	2.5 ± 4.5‡
FVC ≥ 70% (4)	83.3 ± 10.9	–	–	77.0 ± 20.4	−6.3 ± 11.6

The continuous variables are presented as mean ± standard deviation. The numbers in parenthesis indicate the patients analyzed in each group.
*A positive difference means an improvement over baseline; a negative difference means poorer than baseline. †p < 0.0005 in the difference in FVC between initial LFT and after 6 and 12 months of the patients according to the severity of the ILD affectation measured by FVC; ‡p = 0.033 in the difference of FVC between initial LFT and at 24 months of the patients according to the severity of the ILD affectation measured by FVC; FVC: forced vital capacity; ILD: interstitial lung disease.

any event, and despite this significance, the differences did not surpass 10% in any of the cases.

No significant differences were detected in FVC or in DL_{CO} either at the start of treatment or after 6 months between the patients with or without added PAH. No differences were detected in FVC or in DL_{CO} when we evaluated the patients treated for 6 months according to the type of SSc skin affectation (diffuse or limited). Finally, there also were no differences according to the time of evaluating the ILD before the start of treatment nor when contemplating those patients with an evolution less than or equal to one year compared with those that had an evolution greater than one year (table 6), nor when the cut-point was two years of evolution (these data not shown).

3.3. Side Effects

Nineteen (51%) patients presented some type of adverse effect during treatment. In order of frequency, 14 (38%) had infection and in one patient this was the reason for suspending the treatment. Three (8%) patients presented leucopenia, three (8%) lymphopenia and three (8%) presented amenorrhea. Only one patient died during the treatment, specifically six months after the start, due to PAH.

4. Discussion

This study demonstrates that intravenous CYC is effective for stabilizing the pulmonary function parameters of ILD associated with SSc. This affirmation is based on the fact that the difference in the FVC and DL_{CO} values between the start and end of treatment were lower than 10% in all cases. Moreover, this stabilization was maintained during the long-term treatment in the patients treated for 24 months.

CYC is considered the treatment of choice for ILD related with SSc.[14,15] This affirmation is true despite the conclusions of the meta-analysis carried out by Nannini et al.[11] According to this study, CYC did not produce a significant improvement of the pulmonary function parameters (FVC and DL_{CO}) of the patients with ILD associated with SSc who were treated for 12 months. Nevertheless, CYC was shown to be effective in the stabilization of these parameters. Currently, it is believed that the most realistic objective of the treatment of ILD associated with SSc is to avoid the progression of the disease.

It should be taken into account that the patients included for study presented moderate-to-mild ILD according to their FVC and DL_{CO} values. This may have influenced the fact that there are no differences higher than 10% between the baseline values and those obtained after 6, 12 or 24 months of treatment. This fact is repeated in the studies controlled with placebo in which up to half of the patients included had FVC values higher than 70%.[24] On the other hand, the treatment of ILD for 12 months could be insufficient. The time analysis of two prospective studies has demonstrated that, once the treatment is concluded, a functional deterioration occurs, especially in those patients with more severe disease in the beginning.[25,26] The results of our study show that CYC is able to maintain this stabilization until 24 months of treatment. Nevertheless, given its potential toxicity, and similarly as in the treatment of other autoimmune disease (as in the case of lupic nephropathy), in long-term maintenance treatment, other less

Table 6
Baseline pulmonary function study and repeated at 6 months of patients treated with 6 monthly pulses of cyclophosphamide according to evolution time of the ILD at the start of treatment and the extension of the skin affectation

Evolution time of ILD	LFT	At the start of treatment	After 6 months	Difference*
≤ 1 year	FVC (%)	65.8 ± 12.8	66.9 ± 13.9	1.1 ± 3.2
> 1 year		64.8 ± 17.2	63.4 ± 13.9	−1.4 ± 4.3
≤ 1 year	DL_{CO} (%)	70.7 ± 18.8	69.1 ± 19.1	−1.6 ± 4.6
> 1 year		67.5 ± 17.9	70.8 ± 10.8	3.3 ± 4.1†
Type of skin affectation	**LFT**	**At the start of treatment**	**After 6 months**	**Difference***
Diffuse SSc	FVC (%)	68.6 ± 15.3	69.7 ± 13.1	1.1 ± 3.4
Limited SSc		64.5 ± 17.0	62.0 ± 16.5	−2.5 ± 5.1
Diffuse SSc	DL_{CO} (%)	71.9 ± 15.6	68.9 ± 10.6	−3.0 ± 3.1
Limited SSc		64.9 ± 22.1	70.2 ± 22.9	5.3 ± 6.8

Number of patients analyzed: evolution time of ILD ≤ 1 year: 17 patients; evolution time of ILD > 1 year: 13 patients; Diffuse SSc: 18 patients; Limited SSc: 11 patients.
The continuous variables are presented as mean ± standard deviation.
*A positive difference means an improvement over baseline; a negative difference means poorer than baseline. †p = 0.005 between the difference of DL_{CO} between the initial LFT and after 6 months of the patients according to the ILD evolution time; DL_{CO}: CO diffusing capacity; FVC: forced vital capacity; ILD: interstitial lung disease; LFT: lung function test; SSc: systemic sclerosis.

toxic immunosuppressants should probably be used, such as azathioprine. Along this line, two prospective studies have analyzed the effect of the treatment with 6 monthly pulses of CYC followed by oral azathioprine. In both, this therapy was able to maintain the stabilization of FVC and DL_{CO}.[10,27]

With the same intention of reducing the toxicity of CYC, several studies have evaluated the efficacy and safety of mycophenolate mofetil (MMF) in the treatment of ILD in patients with SSc.[28,29] In two retrospective studies that included 13 and 10 patients respectively, MMF improved FVC values after 12 months of treatment. In contrast, DL_{CO} did not change.

In our study, the pulmonary function stabilization does not seem to vary depending on the ILD evolution time nor on the type of cutaneous affectation (diffuse or limited). In fact, the progression of ILD has been related with a premature and severe onset of SSc[30] and with the most severe restrictive form at the moment of diagnosis.[25] The patients with initially more severe disease represented by FVC < 70% were those who presented the greatest improvement at the end of treatment at 6, 12 and 24 months, although the difference was not significant. This data is in line with the stratification system proposed by Goh et al[31] in which the patients with extensive ILD (>20% on high-resolution computed tomography) or those with an indeterminate amount of extension but FVC < 70% are those that present greater mortality and, therefore, would benefit from more aggressive treatment. In this regard there is a certain amount of controversy, as at least one study has demonstrated a better response in patients with early and mild forms of the disease.[26]

As for glucocorticoids, their role in treating ILD has not been established, nor has their initial dose. In a prospective study, high doses (1 mg/ kg/ day) were related with an improvement in FVC, DL_{CO} and dyspnea one year after treatment.[32] In a retrospective study, however, high isolated doses provided no benefit.[33] In addition, it is considered that glucocorticoids at a dose equal to or more than 15 mg/day increase the risk of scleroderma renal crisis.[34] None of the patients in the study presented symptoms suggesting scleroderma renal crisis in spite of the initial treatment of high doses of prednisone.

This present study has some limitations given its retrospective design. First of all, not all the patients had LFT at all the different time points, which reduced the number of patients that could be analyzed. The time of the start of the treatment was based on the criteria of the specialist responsible for each case, which reduced the homogeneity of the sample of our patients. Despite analyzing two patient cohorts, the number of these is limited with the consequent limitations of the comparisons made and of the generalization of the results. Finally, we lacked a control group without treatment, which would have allowed us to determine the natural long-term evolution of ILD in untreated patients.

In conclusion, intravenous CYC administered together with corticoids in this series of patients stabilized the pulmonary function parameters in the long-term treatment of ILD associated with SSc. The patients with severe restriction in the beginning showed greater improvement, but this was less than 10% in all cases.

Conflict of Interest

The authors declare having no conflict of interest.

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