Cyclophosphamide Pulse Regimen in the Treatment of Alveolitis in Systemic Sclerosis

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ABSTRACT. ***Objective.*** To evaluate, in a pilot study, the efficacy of a short term cyclophosphamide (CYC) pulse regimen on alveolitis in a cohort of patients with systemic sclerosis (SSc).

Methods. Twenty-three patients with SSc (17 diffuse SSc and 6 limited SSc) were selected in 5 centers in Italy, based on the findings of an abnormal bronchoalveolar lavage (BAL) cell analysis in association with altered pulmonary function tests (PFT) or recent deterioration in flow volume curve (FVC). Patients were also evaluated by skin score (Rodnan), esophageal manometry and barium swallow radiography, and electrocardiography and 2-mode echocardiography. The pre-enrolment pulmonary evaluation and after 6 months of therapy included evaluation of the clinical status, PFT (FVC, FEV1, DLCO), BAL, standard chest radiograph, and chest high resolution computed tomography. All patients received IV CYC (1000 mg/m^2 of body surface monthly for 6 mo) and oral prednisone (25 mg daily for the first month and subsequently 5 mg daily of maintenance dosage for the remaining 5 mo). A complete blood count and urinalysis were obtained at monthly intervals.

Results. After 6 months of therapy the values for FVC did not change significantly. Individually, 8 of 23 patients showed an improvement (> 15% increase) in FVC after 6 months, while FVC in 13 cases remained stable. Only 2 patients had an important decline in FVC after 6 months of therapy (17 and 24% decrease). Improvement in DLCO was noted in 15 of 23 patients after 6 months of therapy. Four patients were stable and 4 patients had a worsened DLCO at the end of the study. After therapy the mean value of BAL fluid recovery did not change. There was a reduction in total cell number although this value did not reach statistical significance. The levels of neutrophils, eosinophils, lymphocytes, and macrophages did not change significantly. Scans for patients with grades 1, 2, and 3 did not differ significantly after 6 months of therapy, and 14 patients were stable. Changes in appearance, in relation to changes in extent of disease, were seen in 8 patients and consisted of an extension of reticular pattern and transformation from grade 1 to 2 (6/8 patients). All patients showed a ground-glass appearance indicating an acute alveolitis. Improvement in ground-glass was noted in 10 of 23 patients after 6 mo therapy. At the end of the study, 8 patients were stable and 5 patients had a diffusion of the ground-glass to other segments. No side effects were experienced during the treatment except for mild nausea in 4 patients; no patients discontinued therapy during the study.

Conclusion. CYC pulse regimen seems to stabilize alveolitis in the majority of cases. The association of CYC pulsed modality with prednisone may be useful in SSc patients to control disease evolution in the lung. (J Rheumatol 2002;29:731–6)

Key Indexing Terms:
SYSTEMIC SCLEROSIS ALVEOLITIS CYCLOPHOSPHAMIDE

Systemic sclerosis (SSc) affects skin and internal organs, leading eventually to fibrosis[1]. The deterioration of lung function is the most frequent cause of death in SSc[2]: this evidence suggests an early and careful diagnosis of lung involvement to

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avoid the evolution of the disease to interstitial fibrosis and honeycombing[3]. It is well known that alveolitis is the earliest and main event initiating the lung fibrotic process in SSc and other lung diseases[3,4]. For this reason, the treatment of alveolitis may be considered one of the strategic priorities in the treatment of SSc. Treatment of lung involvement in SSc has always been a problematic task with a poor outcome.

At the beginning of the 1990s, cyclophosphamide (CYC) was introduced for treatment of inflammatory involvement of the lung following the experience of idiopathic pulmonary fibrosis. In this disease, where progressive pulmonary insufficiency is due to a fibrotic interstitial process, CYC has proved effective, in particular by intravenous regimen[5]. As reported in systemic lupus erythematosus, this regimen seems better tolerated than oral daily administration, with a lower incidence of toxicity and longterm malignancy[6].

In SSc, CYC was effective in controlling lung involvement[7]. By oral administration, separate groups have shown that CYC is effective in raising pulmonary function tests and lowering acute phase reactants and aminopropeptide type III collagen[8-10]. The problems with longterm oral administration of CYC suggest the pulse regimen as an alternative route of administration for effective treatment for lung inflammation. For this reason, a CYC pulse regimen was employed in 5 patients showing a reduction of severity of dyspnea, but failed to improve flow volume curve (FVC) or diffusion capacity of carbon monoxide (DLCO) or resolve radiologic abnormalities[11]. In another study on 8 patients, a regression of the early phase of lung involvement was seen, without a significant modification of the advanced reticular patterns[12].

We evaluated the efficacy of short term CYC pulse regimen on alveolitis in a larger cohort of patients with SSc.

MATERIALS AND METHODS

Patients. Twenty-three nonsmoking patients with SSc (19 women, 4 men, mean age 57.3 yrs, range 39–67) diagnosed according to American College of Rheumatology criteria[13] were selected from the outpatient clinics of 5 centers in Italy (L'Aquila, Ancona, Firenze, Napoli, Roma). After giving informed consent, patients were enrolled in the study, based on the findings of an abnormal bronchoalveolar lavage (BAL) cell analysis in association with altered pulmonary function tests (PFT) or recent deterioration in FVC. Seventeen patients were classified as having diffuse and 6 as having limited disease[14]. Skin assessment was performed utilizing a modified Rodnan (m-Rodnan) total skin thickness score technique[15]. Patients were evaluated for involvement of the esophagus (manometry, barium swallow radiography), renal system (blood urea, serum creatinine levels, urinalysis), and cardiac system (electrocardiography, 2-mode echocardiography).

Pulmonary evaluation. The pre-enrolment pulmonary evaluation and after 6 months of therapy included clinical status (dyspnea on exertion, nonproductive cough, etc.) and pulmonary function tests, including FVC, FEV1 and DLCO, expressed as percentage of predicted values based on age, sex, and height (techniques accepted by the American Thoracic Society were used for determination of FVC and DLCO[16]). Test results were compared to predicted normal standard values[17]. The following definitions were applied to changes from entry values of FVC or DLCO: improvement: a rise > 15% from baseline values; stability: no change or a change of ± 15% from baseline values; deterioration: a decline of > 15% from baseline values.

Bronchoalveolar lavage. BAL was performed by injection and immediate withdrawal by syringe of 5 × 60 ml boluses of sterile 0.9% sodium chloride solution, all at one site. The recovered BAL fluid was pooled and filtered through a double layer of sterile gauze to remove mucus, then added to an equal volume of Hanks' balanced salt solution (Gibco, Grand Island, NY, USA) and maintained at 4˚C. The fluid was then centrifuged at 500 g for 15 min at room temperature, and the recovered cells were washed and counted; cytocentrifuged smears were stained with Wright's stain for differential cell count. Alveolitis was defined as an increase of > 2 standard deviations (SD) above the mean in the absolute number of alveolar macrophages, neutrophils, and/or eosinophils compared to 60 healthy controls (10 per center) whose results are consistent with results reported by the BAL Cooperative Group Steering Committee[18]. Data from BAL were available for 18 patients. Six patients had inadequate return for interpretation. In all cases, at baseline, the findings were suggestive of acute alveolitis.

Standard chest radiographs. Standard high resolution computed tomography (HRCT) of the chest was performed with third generation CT equipment. The images were obtained with 1 mm collimation and 10 mm intervals at maximal end-inspiratory phase with the patient in supine position using a high spatial frequency algorithm. When necessary, prone scans were added to distinguish gravity related changes from structural abnormalities. Each section was reviewed by 2 blinded radiologists for the presence of and the extent of ground-glass opacities as well as reticular lines/honeycombing. A ground-glass pattern was defined as a patchy or diffuse increase in lung density that did not obscure pulmonary vascular markings, whereas a reticular pattern was defined as the presence of intersecting lines ranging from a fine network to evident honeycombing. HRCT findings were graded[19,20] as follows: grade 1: prevalence of ground-glass opacities; grade 2: ground-glass and reticular pattern equally extensive; grade 3: prevalence of reticular pattern/honeycombing. Disease extent scoring was obtained in each case using a weighting correction factor for differences in lung volumes at each HRCT level, as described[20]. For acute alveolitis (ground-glass appearance), an extent of disease score was generated by localizing each abnormality to the number of bronchopulmonary segments involved, as follows: 1–3 segments: 1 point; 4–7 segments: 2 points; 7–9 segments: 3 points; > 9 segments: 4 points. Followup studies were performed on anatomically comparable sections with the patient in the same (supine/prone) position and photographed at comparable window settings.

Treatment. No patient had been treated with cytotoxic drugs or biologic response modifying agents during the 12 months preceding the study. All enrolled patients received IV CYC (1000 mg/m^2 of body surface monthly for 6 mo) in association with oral prednisone (25 mg daily for the first month and subsequently 5 mg daily of maintenance dosage for the remaining 5 mo). A complete blood count and urinalysis were obtained at monthly intervals. Clinical, PFT, BAL, chest radiographic, and HRCT followup evaluations were performed at the end of the treatment.

Statistical analysis. The nonparametric Wilcoxon 2 tailed test (normal approximation) and the rank correlation test were used when appropriate for statistical analysis.

RESULTS

Pulmonary function tests. PFT results are summarized in Table 1. In our patients, a mild reduction in the FVC was found at the time of study entry, whereas a great variability was observed (91% predicted, 36–123%). As a group, after 6 months of therapy the values for FVC did not change significantly (91% predicted, 39–123%). Individually, 8 of 23 patients showed an improvement (> 15% increase) in FVC after 6 mo, while FVC in 13 cases remained stable. Only 2 patients had an important decline in FVC after 6 mo of therapy (17 and 24% decrease). All patients showed a reduced DLCO: as a group, the value for DLCO in SSc patients was

Table 1. Individual and mean values of pulmonary function tests in patients with SSc.

Patient	FVC (%)		FEV (%)		DLCO (%)	
	Time 0	6 Mo	Time 0	6 Mo	Time 0	6 Mo
1	101.22	100.32	97.24	97.17	54	58
2	99.7	100.2	104.7	105.1	44	60
3	106.2	106.9	98.22	96.94	50	52
4	99.71	100.44	104.31	104.51	42	50
5	123	106	99.4	100.1	51	51
6	91.4	105	96.2	99.4	44	57
7	94.3	92.1	91.2	88.2	51	54
8	101.7	100.4	101.2	101.8	74	70
9	84.3	95.1	76.3	85.4	31	50
10	70.2	80.4	72.0	74.3	65	87
11	61.3	64.2	60.3	68.4	19	47
12	86	87	83.4	86.2	60	51
13	93	86	97.7	90.1	59	62
14	89	103	74.3	76.2	41	62
15	40	50	43.1	53.8	49	60
16	98	89	88	82	55	47
17	85	88	87	95	66	79
18	36	40	33	41	24	40
19	81	97	85	99	50	60
20	81	93	77	86	23	47
21	66	72	76	82	40	52
22	91	123	90	102	40	58
23	60	39	84	73	54	47
Medians (ranges)	91 (36–123)	91 (39–123)	88 (33–128)	86 (41–105.1)	50.5 (19–88)	64.5 (47–87)
	$p > 0.05$		$p > 0.5$		$p > 0.05$	

50.5% predicted (19–88%). After 6 mo of treatment we observed an increase in this value (64.5% predicted, 47–87%), although it did not reach statistical significance. Improvement in DLCO was noted in 15 of 23 patients after 6 mo of therapy. Four patients were stable and 4 patients had a worsened DLCO at the end of the study.

Bronchoalveolar lavage. BAL analyses of SSc patients at entry and after 6 mo of therapy are shown in Table 2 and the individual values are summarized in Figure 1. Abnormalities were observed in all patients whose BAL was analyzed. SSc patients showed: (1) a significantly lower recovery of BAL fluid compared to controls (53%, 30–60% vs 72%, 60–82%, respectively; $p < 0.005$). After therapy, the mean value of BAL fluid recovery did not change (49%, 30–70%). (2) A significantly higher total cell count compared to controls (46.0×10^4 cells/ml, $12.9–73.0 \times 10^4$ cells/ml vs 17.5×10^4 cells/ml, $7.0–19.3 \times 10^4$ cells/ml, respectively; $p < 0.005$). After therapy, a reduction of cell number was observed, although this value did not reach statistical significance (28.5×10^4 cells/ml, $5.6–68.0 \times 10^4$ cells/ml). (3) At entry, SSc patients had a significantly greater number of neutrophils compared to controls (4%, 0–28% vs 1%, 0–1% respectively; $p < 0.001$), eosinophils (0.4%, 0–26% vs 0.1%, 0–1% respectively; $p < 0.005$), a higher percentage of alveolar lymphocytes (16%, 6–77% vs 8%, 3–8%, respectively; $p < 0.005$), and alveolar macrophages (30.0×10^4, $17–40.0 \times 10^4$ vs 13.0×10^4, $8.5–16.4 \times 10^4$, respectively; $p < 0.001$). After therapy, none of these values changed significantly.

High resolution computed tomography. Global CT appearances at initial scanning were categorized as: (1) grade 1 (prevalence of ground-glass opacities) in 14 patients; (2) grade 2 (ground-glass and reticular pattern equally extensive)

Table 2. Bronchoalveolar lavage findings at entry and after 6 months of therapy.

Time	0	6 Mo	p
Recovery, %	53 (30–60)	49 (30–70)	NS
Cells/ml	460,000 (129,000–730,000)	285,000 (56,000–68,000)	NS
Macrophages,%	62 (21–85)	78 (18–81)	NS
Lymphocytes, %	16 (6–77)	12 (5 –80)	NS
Neutrophils, %	4 (0–28)	3 (0-11)	NS
Basophils, %	0 (0–0.5)	0.5 (0–1)	NS
Eosinophils, %	0.4 (0–26)	1 (0–8)	NS

NS: not significant.

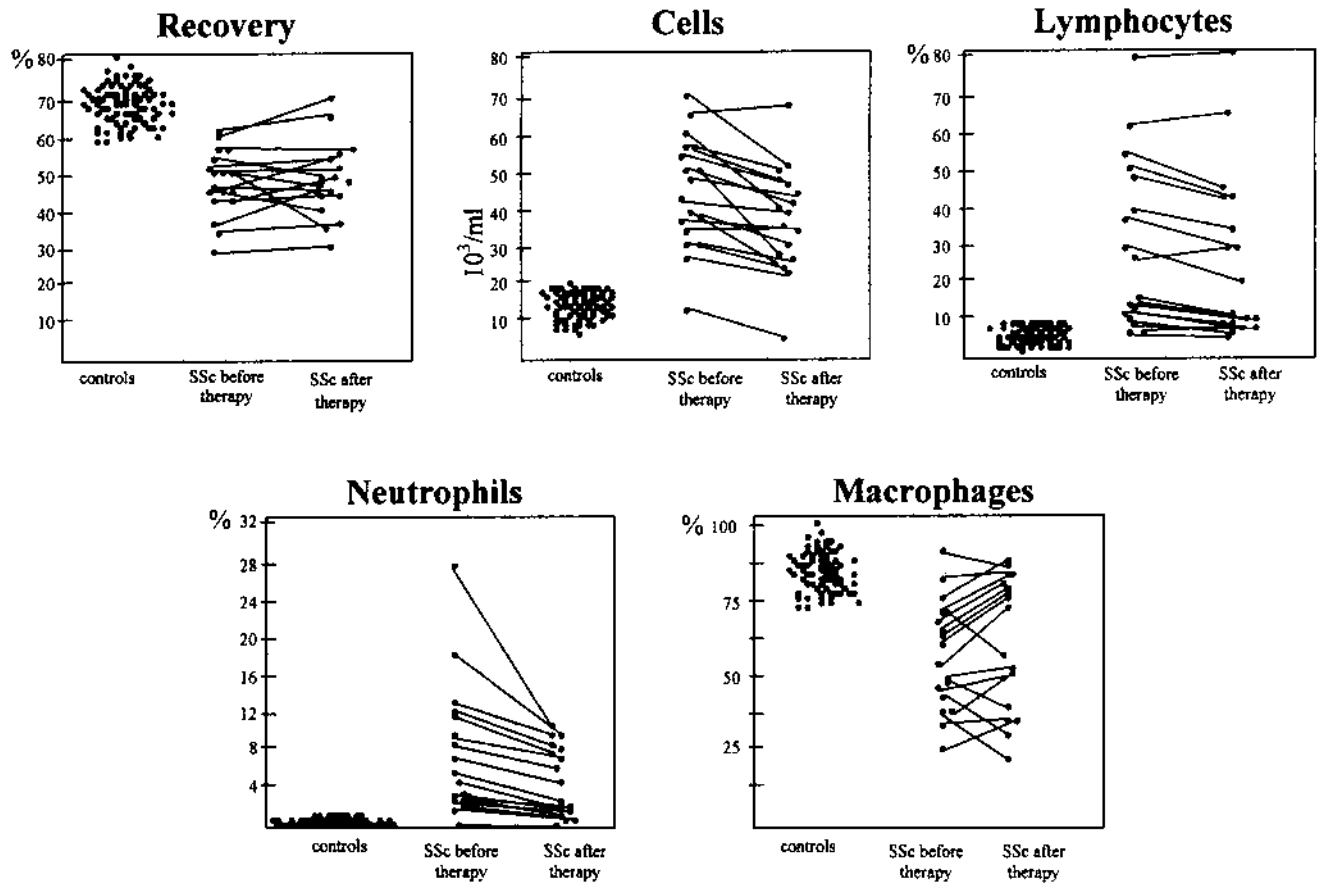

Figure 1. The individual values of the assessed variables evaluated in BAL. As a group, no variables reach statistical significance compared to controls.

in 6 patients; and (3) grade 3 (prevalence of reticular pattern/honeycombing) in 3 patients. As shown in Figure 2, scans for patients with grades 1, 2, and 3 did not differ significantly after 6 mo of therapy. In fact, a majority of patients (14) were stable. Changes in appearance, in relation to changes in extent of disease, were seen in 8 patients and consisted more commonly of an extension of reticular pattern and transformation from grade 1 to 2 (6/8 patients).

At HRCT, all patients showed a ground-glass appearance, indicating acute alveolitis. As a group, the value for severity score in SSc patients was 3.5 (1–4). After 6 months of treatment we observed a decrease in this value (2, 1–4), although this difference did not reach statistical significance. Improvement in ground-glass was noted in 10 out of 23 patients after 6 mo of therapy: at the end of the study, 8 patients were stable and 5 patients had a diffusion of the ground-glass to other segments (Figure 3).

After treatment, no correlation was found among HRCT scores and BAL (both number of cells and fluid recovery).

The results show that the large majority of patients, independent of the limited and diffuse form of SSc, improved or remained stable under CYC treatment. Moreover, those patients characterized by the deterioration of a variable after treatment also showed deterioration of all other variables investigated.

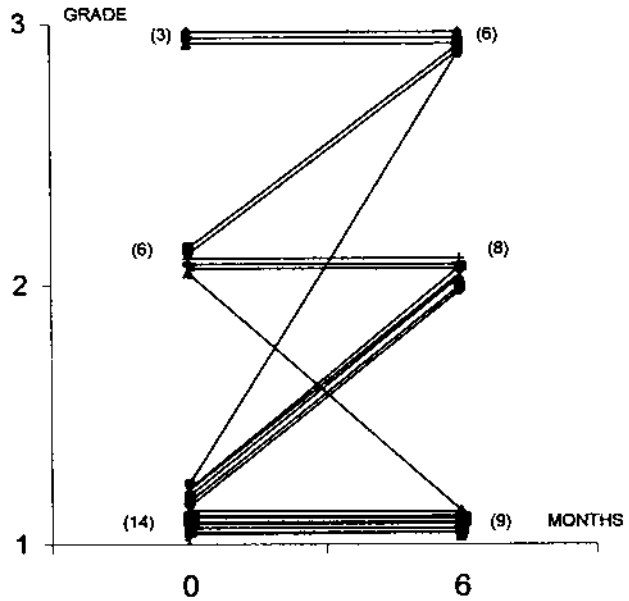

Figure 2. The evolution of pulmonary grading by HRCT in 23 SSc patients. After 6 mo of therapy, 14 patients were stable (number of patients in parentheses).

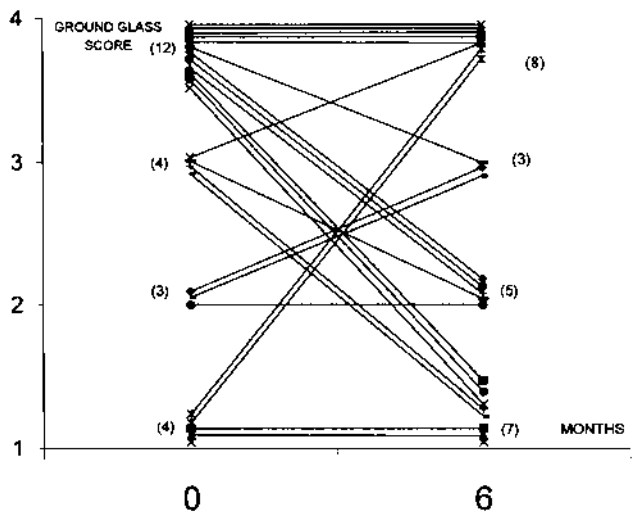

Figure 3. Modification of the ground-glass extent of the disease score, by pulmonary HRCT, in 23 SSc patients. Eight patients were stable and 10 patients showed a decrease of ground-glass extension after therapy (number of patients in parentheses).

Short term safety. No side effects were experienced during the treatment except a mild nausea in 4 patients: no patient discontinued therapy during the study.

DISCUSSION

Several drugs have been unsuccessfully employed to fight lung involvement in SSc. The current pilot study was specifically designed to assess, in a short period of time (6 mo), the effects of CYC pulse intermittent regimen plus low doses of prednisone on functional, morphological, and biological aspects of alveolitis during SSc, also in the absence of clinical symptoms of acute lung disease. Further, no correlation was found between the skin score, which showed moderate values (19, 4–32), the positivity for anti-topo-1 autoantibody, which greatly increases the risk of pulmonary fibrosis (15 with diffuse SSc and 1 with limited disease), and either the pulmonary function tests or BAL results. Thus, on the basis of these findings and nearly normal FVC, it is difficult to assess whether our patients displayed a relatively mild disease, probably a disease with a benign course, or alternatively, an early phase of SSc related lung fibrosis.

Our data clearly show that this association, after 6 months of treatment, significantly improves or stabilizes the function of SSc lungs. In some types of idiopathic pulmonary fibrosis, which display several analogies with SSc lung fibrosis, the CYC pulse regimen achieved a significant increase of FVC[5]. In our SSc patients, CYC plus prednisone did not change FVC but, at least in part, improved DLCO. Although this finding could be related to the nearly normal values observed in our patients, these results are partially in agreement with 2 studies that used the CYC pulse regimen in SSc lung disease. Varai, *et al* treated 5 patients for 1 year with CYC (1 g/mo), but found no significant increase of FVC[11]; Davas, *et al* treated 8 patients with CYC for 1 year (750 mg/m^2/mo) and prednisone (10 mg), showing an increase of DLCO after 6 and 12 mo, and of FVC after 12 mo[12]. Studies with oral CYC showed an amelioration of FVC but no significant improvement of DLCO after 6 mo[8] and 1[9] and 2[10] years. Recently, White, *et al* in a retrospective study observed a stabilization or improvement of FVC and DLCO after 16 mo of followup[21]. Davas, *et al* reported a lack of efficacy of oral CYC on FVC, but a significant rise in DLCO after 12 mo of treatment[12].

In our patients, alveolitis was identified through biological variables, represented by determination of the percentage of cells present in the BAL. In our patients, 6 mo of treatment did not modify the total recovery of the BAL fluid, which was significantly reduced at entry, compared to healthy controls, but these data could be related to airway collapse due to bronchiolectasis, which is frequent in SSc, and all the other assessed variables (total cell count, macrophages, lymphocytes, neutrophils, eosinophils, and basophils). After a year of CYC pulse regimen in 5 patients, Varai, *et al* found a decrease of 51% of lymphocytes in the BAL but no change in the percentage of neutrophils[11].

We observed a trend after therapy toward a lower number of total cells, although these values did not reach statistical significance. Unfortunately, in the studies on oral CYC, BAL was never performed after the treatment[8-10].

The morphological data obtained with HRCT are partially in agreement with data reported by others. Davas, *et al* performed HRCT before treatment and after 6 and 12 mo of CYC pulse regimen, grading lung involvement with the Wells system[20]: they found that 6 out of 7 patients scored as grade 1 (ground-glass only) displayed a reduction of ground-glass extension, while only 1 patient showed a complete resolution at 6 and 12 mo[12]. The only patient showing a grade 3 did not change after 6 and 12 mo of pulse CYC regimen. Our results partially confirm the observation of Davas, *et al* regarding the grade 1 patients. Our results clearly show that patients with a specific pattern (reticular, honeycombing, etc.) and scored with the appropriate grade are likely to remain in that grade or may evolve to a more severe one. Therapy seems unable to reverse this trend. This result seems corroborated by the very recent data of Pakas, *et al* showing that no change in the percentage of reticular involvement was obtained after pulse cyclophosphamide and prednisolone for 12 months[22]. Indeed, only 1 patient, scored as grade 2, showed an amelioration going to a lower grade. In a large number of patients, the ground-glass extension was reduced, involving a lower number of lung segments, but never completely solved. These findings suggest that the pulmonary lesions were not completely reversible, and CYC plus prednisone may more likely stabilize the radiological pattern than completely clean the lung, as observed by HRCT. After 12 months, Pakas, *et al* obtained instead a regression of ground glass opacities in more than 50% of cases[22]. This discrepancy with our data seems most likely due to the fact that Pakas, *et al* pulsed cyclophosphamide for 12 months along with high doses of prednisolone.

The use of CYC in SSc has been suggested by the previous successful use in idiopathic pulmonary fibrosis[5,23]. Indeed, experiences with oral versus intravenous CYC in idiopathic pulmonary fibrosis showed that the pulse regimen was better tolerated, with a lower longterm risk of malignancy[6,24]. In these studies, prednisone was employed as a support drug to CYC, showing a survival advantage at 3 years compared to the survival of patients enrolled in studies not employing steroids. Silver, *et al* used prednisone at a dosage ranging from 5 to 40 mg daily as a support drug to the oral CYC, obtaining only the improvement of FVC after 6 mo of therapy[8]. Steen, *et al* used a daily dose of prednisone lowered to 10 mg, with a significant improvement of FVC but not DLCO[10]. Akesson, *et al* started prednisone at 30 mg daily, tapering it to 5 and 10 mg every other day, and obtained a significant rise of FVC[9]. In our study, a similar approach to that of Akesson, *et al* was chosen, with a starting dose of prednisone 25 mg, which was progressively tapered to 5 mg, until the end of the study. Unfortunately, our study and previous reported works were unable to determine the role of prednisone on lung function and if it should be considered a support drug. Recently it has been reported that oral CYC is of limited efficacy in idiopathic pulmonary fibrosis in patients who failed to respond to or who experienced adverse effects from corticosteroid treatment[25].

In our cases CYC pulse regimen plus oral prednisone seem to freeze the lung involvement, stabilizing the clinical picture found in the pretreatment period in the majority of cases. Thus, this association may be useful in SSc patients to control disease evolution at the lung level. However, some points need still to be addressed, such as the monthly dosage of CYC and the therapeutic role of low dose prednisone to support the CYC. On these grounds, a randomized double blind study with pulse CYC and steroids is warranted, to determine the real efficacy and utility of this therapy in controlling lung involvement of SSc.

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Correction

Cyclophosphamide Pulse Regimen in the Treatment of Alveolitis in Systemic Sclerosis

Giacomelli R, Valentini G, Salsano F, Cipriani P, Sambo P, Conforti ML, et al. Cyclophosphamide pulse regimen in the treatment of alveolitis in systemic sclerosis. J Rheumatol 2002;29:731-6. The correct name of the co-author M. Proietti is Michele Proietti.

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