Cyclophosphamide with Low or High Dose Prednisolone for Systemic Sclerosis Lung Disease

IOANNIS PAKAS, JOHN P.A. IOANNIDIS, KATERINA MALAGARI, FOTINI N. SKOPOULI, HARALAMPOS M. MOUTSOPOULOS, and PANAYIOTIS G. VLACHOYIANNOPOULOS

ABSTRACT. ***Objective.*** To evaluate the safety and efficacy of monthly intravenous pulses of cyclophosphamide (CP) in combination with low or high doses of prednisolone in patients with systemic sclerosis (SSc) related interstitial lung disease (ILD) with FVC < 70% of predicted.

Methods. An open label, non-parallel arm study, performed in the rheumatology outpatient clinic of a university hospital. Twenty-eight patients with SSc related ILD were evaluated. Endpoint evaluations included the evolution of high resolution computed tomography, pulmonary function tests, skin involvement and dyspnea over 12 months. Patients were treated with monthly IV CP in combination with prednisolone at low (< 10 mg/day; n = 12) or high doses (1 mg/kg/day for 4 weeks, then reducing the prednisolone by 5 mg/day on alternating days each 2 weeks; n = 16).

Results. In the low dose steroid group, no improvement was seen for any endpoint at 6 and 12 months of followup. In the high dose steroid group, at 12 months there was significant improvement in the percentage of "ground glass" parenchymal lung involvement (–5.7%; p = 0.003), as well as in the percentage of predicted FVC (12.4%; p < 0.001), the percentage of predicted DLCO (7.3%; p = 0.029), the percentage of skin involvement (–5.4%; p = 0.01), and the severity of dyspnea (p = 0.012). Substantial improvement was seen as early as 6 months. One patient (low dose group) died from ILD.

Conclusion. A combination of IV pulse CP with high doses of prednisolone shows promising efficacy in improving the clinical, physiological, and radiological evolution of SSc related ILD with reversal of the underlying alveolitis. (J Rheumatol 2002;29:298–304)

Key Indexing Terms:
PULMONARY SYSTEMIC FIBROSIS SYSTEMIC SCLERODERMA THERAPY
INTRAVENOUS CYCLOPHOSPHAMIDE PREDNISOLONE

Interstitial lung disease (ILD) is a well recognized manifestation of scleroderma (systemic sclerosis, SSc)[1-4]. ILD is now the most frequent cause of death in these patients[5,6] since angiotensin-converting enzyme inhibitors have reduced the renal crisis related mortality[7]. SSc related ILD resembles idiopathic pulmonary fibrosis (IPF). In both conditions the initiating event appears to be an inflammatory reaction to the alveolar wall (alveolitis), which progresses to fibrosis[8]. Once established, interstitial fibrosis is resistant to current treatment modalities. Therefore, aggressive therapy with immunosuppressive agents is likely to be most efficacious early in the course of the disease[9]. The development of new diagnostic methods such as bronchoalveolar lavage (BAL) and high resolution computed tomography (CT) allows the identification of SSc related ILD at earlier stages[10-12].

To date, treatment attempts with ILD have been disappointing or of limited success[13-23]. Oral cyclophosphamide (CP) has shown some promise[19-21], but it is associated with serious side effects[22,23]. Intravenous pulse CP is effective and better tolerated than daily oral doses in the treatment of other rheumatologic conditions[24-28]. As well, IV pulse CP has been reported to be of some value in IPF[29,30], a condition where corticosteroids are the standard of care. The results of 2 pilot studies assessing the efficacy of IV pulse CP for SSc related ILD or other collagen vascular diseases were controversial[31,32]. Neither study determined whether low or high dose steroids may enhance the efficacy of IV pulse CP.

New regimens need to be tested for the treatment of SSc related ILD. Given the accumulated experience, we evaluated the clinical utility of IV pulse CP combined with low or high dose prednisolone in this setting through a prospective open label study.

From the Department of Pathophysiology, School of Medicine, National University of Athens, Athens; the Clinical and Molecular Epidemiology Unit and Clinical Trials and Evidence-Based Medicine Unit, Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, Ioannina; Harokopion University, Athens; the Department of Radiology, Evangelismos Hospital, Athens, Greece; and the Department of Medicine, Tufts University School of Medicine, Boston, Massachusetts, USA.

I. Pakas, MD; H.M. Moutsopoulos, MD; P.G. Vlachoyiannopoulos, MD, Department of Pathophysiology, School of Medicine, National University of Athens; J.P.A. Ioannidis, MD, Department of Hygiene and Epidemiology, University of Ioannina School of Medicine and Department of Medicine, Tufts University School of Medicine; K. Malagari, MD, Department of Radiology, Evangelismos Hospital; F.N. Skopouli, MD, Harokopion University.

Address reprint requests to Dr. P.G. Vlachoyiannopoulos, Department of Pathophysiology, School of Medicine, National University of Athens, 75 Mikras Asias Str, 115 27 Athens, Greece. E-mail: pvlah@med.uoa.gr

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MATERIALS AND METHODS

Inclusion criteria. Twenty-eight consecutive consenting patients with SSc and evidence of pulmonary interstitial involvement were included in this trial. All patients fulfilled the American College of Rheumatology criteria for the classification of SSc[33]. Patients were classified as having diffuse or limited cutaneous SSc[34]. Patients gave written consent. All patients were followed in the Department of Pathophysiology, Laikon General Hospital, National University of Athens. Patients had to meet the following criteria establishing the diagnosis of ILD and excluding other conditions: (1) FVC < 70% of predicted; (2) FEV_1/FVC > 70% of predicted (to exclude patients with significant obstructive pulmonary disease); and (3) no history of an occupational exposure or any other disorder that might adversely affect pulmonary function, such as myocardial infarction, congestive heart failure, severe valvular disease, emphysema, or isolated pulmonary hypertension. Patients with impaired renal function (creatinine clearance < 40 ml/min) were excluded to avoid cyclophosphamide toxicity. Previous therapy with other immunosuppressive agents had to be withdrawn for at least 4 weeks prior to study entry and doses of steroids during this same washout period were not to exceed the equivalent of 10 mg/day prednisolone.

Study design. In this one year prospective open label study, patients who satisfied entry criteria received either of the following regimens: (1) Low dose steroid group (12 patients): IV pulse CP monthly for 6 mo and bimonthly for another 6 months, plus low dose oral prednisolone (< 10 mg/day throughout the study). (2) High dose steroid group: IV pulse CP monthly for 6 mo and bimonthly thereafter, plus high dose prednisolone [1 mg/kg/day (maximum 60 mg/day) for 4 weeks; then reducing the prednisolone by 5 mg/day on alternating days each 2 weeks]. Once monthly IV pulse CP was dosed at 500 mg/m^2 initially, followed by 750 mg/m^2 one month later (maximum 1500 mg per pulse). The drug was administered in 500 ml of 5% glucose solution over 90 min. Peripheral blood cell counts were monitored routinely, with dosage adjustments if the total leukocyte count fell below 3000/mm^3. IV pulse CP was accompanied by 2 doses of 4 mg of ondansetron intravenously. For the prevention of cystitis, Mesna (Urometexan) was given intravenously in 3 separate doses. The allocation of patients in each group was not parallel: patients in the high dose steroid group were consecutively selected when the low dose steroid group had completed at least 6 consecutive months of therapy. This approach was chosen based on reports[12,35] that suggested that patients with IPF who are going to improve do so by 6 months of therapy, and on our preliminary data from the low dose group of patients[36], which showed that patients receiving IV pulse CP with low dose steroids over the first 6 months did not improve substantially.

Background study evaluation. History and physical examination were performed at study entry, at monthly intervals for the first 6 months, and bimonthly thereafter. One physician was responsible for selecting patients, keeping the records, and managing patients' problems related either to their disease or to their therapy. As part of a comprehensive initial evaluation, extrapulmonary disease manifestations were sought by electrocardiograms, echocardiography, manometry of the esophagus, and kidney function tests. Laboratory variables including a complete blood cell count, kidney and liver function tests, and urinalysis were performed at each assessment. Immunologic evaluations of the patients including antinuclear antibodies (ANA), anticentromere antibodies (ACA) by immunofluorescence using HEp-2 cell substrate, antibodies to U1 ribonucleoprotein (U1RNP), Ro/SSA, La/SSB, and anti-topoisomerase I by counterimmunoelectrophoresis and Western blotting were performed at study entry.

Endpoints. The primary endpoint for both groups was the evolution of high resolution CT scan findings at 12 months compared to baseline. The extent (percentage) of "ground glass" involvement, reticular pattern involvement, and their sum (composite interstitial disease score) were assessed.

Secondary endpoints addressed the changes in pulmonary function test measures (FVC, TLC, DLCO) and changes in the grade of dyspnea severity. We also assessed changes in the extent of skin involvement. These variables were assessed at comparisons of baseline with 6 and 12 month values. Since the selection of patients was based on a low FVC, comparisons for this variable are subject to regression-to-the-mean bias, but the change from 6 to 12 months is not affected.

Evaluation of endpoint variables. Skin score. Skin involvement was assessed by palpation at each patient visit using the modified 17 site Rodnan skin score[37]. The 17 sites evaluated included the face and neck, anterior chest, anterior abdomen, upper arms, forearms, dorsum of the hands, fingers, thighs, calves, and dorsum of the feet. Each site was graded on a 0–3 scale as described[37]. Individual zones were summed to obtain a total skin score (maximum possible score = 51). Each patient was evaluated by the same physician at all visits. Values of skin score at each evaluation, and not mean values or the peak score, for each patient were recorded for analysis.

Dyspnea. Symptoms of exertional dyspnea (ED) were scored at each patient visit on a 7 point scale as follows: 0 = none, 1 = ED after 2 flights of stairs, 2 = ED after one to 2 flights of stairs, 3 = ED with one flight of stairs, 4 = ED less than one flight of stairs or on the flat at own pace, 5 = ED on minimal exertion, and 6 = ED at rest.

Pulmonary function tests. Lung function testing was performed at study entry and at 6 and 12 months of treatment. Spirometric evolution (Tranifer screen II/Q; Erich Jaeger, Germany) included the determination of FVC and FEV_1. TLC was measured by the helium dilution technique and carbon monoxide diffusion capacity (DLCO) using the single breath method. Results were expressed as a percentage of predicted values for spirometric tests[38] and for TLC and DLCO.

High resolution CT. CT of the chest was performed at entry and the end of the study. Thin section of 1 mm thickness of the thorax was taken with a high resolution algorithm at maximum inspiration, with 10 mm intervals extending from the apex to the base of the lung. A limited number of sections were also performed through the lower zones of the lung with the patient in prone position to exclude false positives from gravity dependent densities. Each individual section on the CT scan was assessed for the presence, pattern, and distribution of interstitial disease. On the basis of the close association between the CT findings and lung histology[39], 2 distinct patterns of abnormal appearance on CT scan were assessed: (1) a ground glass pattern (GGP), defined as hazy increased density of lung parenchyma reflecting increased cellularity; and (2) a reticular pattern (RP), defined as thickened septal or subpleural lines or parenchymal subpleural linear bands and honeycombing, corresponding to fibrotic histology findings. GGP strictly confined around areas of traction bronchiectasis was not recorded as GGP, but fine reticulation was the preferred characterization[40]. Each CT scan was assessed at 5 levels — the origin of the great vessels, middle of the aortic arch, main carina, pulmonary venous confluence, and 1 cm above the right dome of the diaphragm. Each CT scan was evaluated by a radiologist blinded to the patient's clinical status and independently by a second investigator. Minor discrepancies were resolved by consensus. A visual estimation method[41] was used to assess the extent of each distinct abnormal pattern separately. The resulting estimates represented the percentage of lung parenchyma that showed evidence of GGP (GGP score) or RP (RP score) roughly to the nearest 5% of total parenchymal involvement. GGP score and RP score were added to give an interstitial disease score (ID score). Overall lung involvement was calculated by averaging the percentages for each zone.

Statistical analysis. The main comparisons involved baseline and followup (6 or 12 month) values. Continuous measures were compared with paired t tests, and dyspnea grade was compared using McNemar's test. The study did not primarily aim at comparing the low dose versus the high dose group directly, but baseline characteristics were compared with similar tests to evaluate whether the 2 groups differed in important baseline measures. To adjust for differences in the baseline extent of lung disease in the 2 groups, in secondary analyses we also fitted regression models using data from both groups. CT scan of lung involvement at 12 months was the dependent variable and baseline CT scan scores as well as treatment by baseline CT scan

scores were the predictors we considered. The interaction term was more important than treatment alone in multivariate models and the treatment terms were dropped from all models. Models with or without constant term gave similar results and only the latter are reported. All analyses were run in SPSS 9.0 (SPSS Inc., Chicago, IL, USA) and all reported p values are 2 tailed.

RESULTS

Baseline characteristics. Twelve patients (10 women, 2 men, mean age 48.6 yrs, SD 12.3) were enrolled in the low dose steroid group and 16 patients (13 women, 3 men, mean age 48.1 yrs, SD 14.1) in the high dose steroid group. Followup CT scan examination was performed on all patients at 12 months, with the exception of one in the low dose group who died 12 months after entry into the study. Nine patients in the low dose group were positive for antitopoisomerase I, one patient had U1RNP specificity, and one had anti-Ro specificity. In the high dose group, 14 patients had antitopoisomerase I specificity. Table 1 summarizes other information on baseline characteristics of patients. Patients in the low dose group had more extensive disease, as manifested by a significantly larger average percentage of reticular lung involvement, which also translated into a significantly larger composite interstitial disease score on the CT scan. The difference in percentage of ground glass lung involvement did not reach formal statistical significance, but it seemed to be equally important in absolute magnitude. Of note, 5 patients in the low dose group had at least 5% of the lung parenchyma with honeycomb appearance, while this was not seen in any patient of the high dose group. A marginal difference also existed in baseline DLCO between the 2 groups. Finally, dyspnea tended to be more severe on average in the low dose group, where there were 3 patients with grade 5, 2 with grade 4, 3 with grade 3, and 4 with grade 1 dyspnea. In the high dose group, only one patient had grade 5 dyspnea, 3 had grade 4, 4 had grade 3, 5 had grade 2, and 3 had grade 1.

Response to therapy: low dose steroid group. As shown in Table 2, no improvement was seen in any of the primary or secondary endpoints in this group over the 12 month followup. Indeed, the percentage of reticular pattern lung involvement increased significantly compared with baseline. There was very limited, nonsignificant improvement in the percentage of ground glass appearance. No pulmonary function measure improved over the study period and there was also no significant improvement in the skin score. For clinical symptoms of dyspnea, both at 6 and at 12 months, 5 patients improved, 2 got worse, and 5 did not change compared to baseline (p = 0.45).

Response to therapy: high dose steroid group. The high dose group showed significant improvements at 12 months in the percentage of ground glass involvement and in the composite interstitial disease score (Table 3). Average ground glass involvement decreased by about 60%. There was no apparent change in the percentage of reticular involvement.

Table 2. Responses to treatment in the group receiving cyclophosphamide plus low dose prednisolone.

Variable	6 mo vs Baseline Mean Change	p	12 mo vs Baseline Mean Change	p
CT scan findings				
Ground glass, %	ND	ND	–1.1	0.64
Reticular pattern, %	ND	ND	+5.9	0.046
Interstitial disease score, %	ND	ND	+4.8	0.20
Pulmonary function tests				
TLC, % predicted	–2.8	0.40	–1.0	0.75
FVC, % predicted	+3.1	0.22	–0.7	0.72
DLCO, % predicted	+2.4	0.66	+0.9	0.83
Skin involvement score	–0.5	0.76	–0.7	0.81

ND: no data collected.

Table 1. Baseline characteristics in the 2 study groups: mean values (SD).

	Low Dose (n = 12)*	High Dose (n = 16)**	p (comparison)
Disease duration, months			
From first reported symptom	73.0 (56.7)	50.6 (43.2)	0.24
From first non-Raynaud symptom	58.5 (52.1)	36.0 (28.6)	0.16
From first clinic visit	25.3 (26.3)	20.1 (23.3)	0.59
Skin involvement	16.0 (9.5)	18.8 (9.2)	0.45
CT scan findings, %			
Ground glass	13.3 (14.5)	9.4 (6.4)	0.35
Reticular pattern	26.3 (12.0)	16.7 (11.2)	0.038
Composite interstitial score	39.6 (21.4)	26.1 (12.3)	0.046
Pulmonary function tests			
TLC, % predicted	60.7 (12.5)	65.4 (8.4)	0.28
FVC, % predicted	54.8 (14.1)	57.5 (9.5)	0.56
DLCO, % predicted	38.2 (16.2)	48.3 (11.3)	0.093

* Including 8 patients with diffuse and 4 with localized scleroderma; ** including 11 patients with diffuse and 5 with localized scleroderma.

Table 3. Responses to treatment in the group receiving cyclophosphamide plus high dose prednisolone.

Variable	6 mo vs Baseline Mean Change	p	12 mo vs Baseline Mean Change	p
CT scan findings				
Ground glass, %	ND	ND	–5.7	0.003
Reticular pattern, %	ND	ND	–0.3	0.88
Interstitial disease score, %	ND	ND	–6.0	0.026
Pulmonary function tests				
TLC, % predicted	–1.2	0.67	+5.1	0.018
FVC, % predicted	+7.6	0.025	+12.4	<0.001
DLCO, % predicted	+1.7	0.36	+7.3	0.029
Skin involvement score	–4.9	1.9	–5.4	0.010

ND: no data collected.

Pulmonary function tests showed consistent patterns of improvement. DLCO did not change significantly at 6 months ($p = 0.36$), but it improved significantly between 6 and 12 months ($p = 0.009$). The FVC improved significantly at 6 months and improved further from 6 to 12 months. Although the first improvement could be biased from the expected regression-to-the-mean, the improvement between 6 and 12 months is not affected by this bias. Total lung capacity also showed trends for improvement between months 6 and 12 ($p = 0.26$) and seemed overall improved between baseline and month 12 ($p = 0.02$).

The skin score improved significantly over the first 6 months and remained at the same levels thereafter for the remaining 6 months of the study. Significant improvements in dyspnea were seen as early as 6 months and persisted at 12 months. By 6 months, 9 patients had improved, one had worsened, and 6 had similar symptoms compared to baseline ($p = 0.022$). In the subsequent 6 months, 5 patients continued to improve, while the other 10 had no change ($p = 0.063$). In all, between baseline and 12 months later, 10 patients improved, one worsened, and 4 had the same severity of symptoms ($p = 0.012$).

Adjusted evaluation of CT scan indices. In regression analysis adjusting for the baseline ground glass percentage, the ground glass percentage at 12 months was predicted by the treatment group ($p = 0.012$ for treatment group by baseline ground glass percentage interaction; Figure 1A). Similarly, adjusting for baseline interstitial disease score, the interstitial disease score at 12 months was predicted by the treatment group ($p = 0.009$ for treatment group by baseline interstitial disease score interaction; Figure 1B). These data suggest that given the same extent of CT scan involvement at baseline, the high dose group tended to have a better response than the low dose group.

Safety. One patient in the low dose steroid group died from endstage ILD during the study. Therapy was overall well tolerated in both groups. No patient withdrew from the study because of adverse events or safety issues. The most common side effects were nausea and vomiting, typically lasting for one to 3 days and controlled by antiemetics. No patient developed leukopenia (total white blood cell count < 3000 cells/mm^3) or other cytopenia. No patient developed scleroderma related renal crisis during the study. All patients of the high dose steroid group and none of the low dose group developed a cushingoid appearance during the first months of the study. One patient experienced transient shortness of breath despite improving pulmonary function measures while taking high dose steroids; her complaints disappeared with the scheduled prednisolone tapering and the symptoms were attributed to muscle weakness due to prednisolone. Blurring of vision due to cataracts was reported by 4 patients, 2 of whom had preexisting cataracts. One patient in the low dose group was given a trial of IV pulse CP in combination with high dose prednisolone 3 years after completing study treatment as an attempt to control the progression of lung disease, and she developed an exacerbation of hypertension and a creatinine of 2.4 mg/dl from a baseline of 1.4 mg/dl. Three patients in the low dose group presented with lower respiratory tract infections, which were treated successfully by antimicrobial chemotherapy. One of these patients experienced the infection 2 months after the end of CP treatment. One patient developed microscopic hematuria 15 months after starting therapy. Although cystoscopy did not reveal findings of cystitis, random biopsies of urothelium were indicative of CP related cytotoxic damage.

DISCUSSION

We assessed the efficacy and safety of intermittent IV pulse CP combined with low or high dose prednisolone in SSc related interstitial lung disease. To our knowledge, this is the largest study evaluating IV pulse CP in this setting. Significant improvement in both the primary (evolution of high resolution CT scan) and secondary (changes in pulmonary function tests, PFT) endpoints was noted in patients where IV pulse CP was combined with high doses of prednisolone. However, the scoring of the CT scans was approximated to 5% and the total amount of change that occurred was on average less than 10%. Therefore, despite evidence for statistically significant improvement, more data are needed to ensure that these changes are also clinically important in the long term. Studies on the natural history of scleroderma lung disease have shown that the overall progression of the disease is indolent, but with substantial individual variability[42]. This variability makes interpretation of the results of therapeutic studies difficult. Nevertheless, patients treated with IV pulse CP and low dose prednisolone showed no improvement in any of the primary or secondary endpoints. Moreover, a significant decrease of respiratory symptoms and skin thickness was

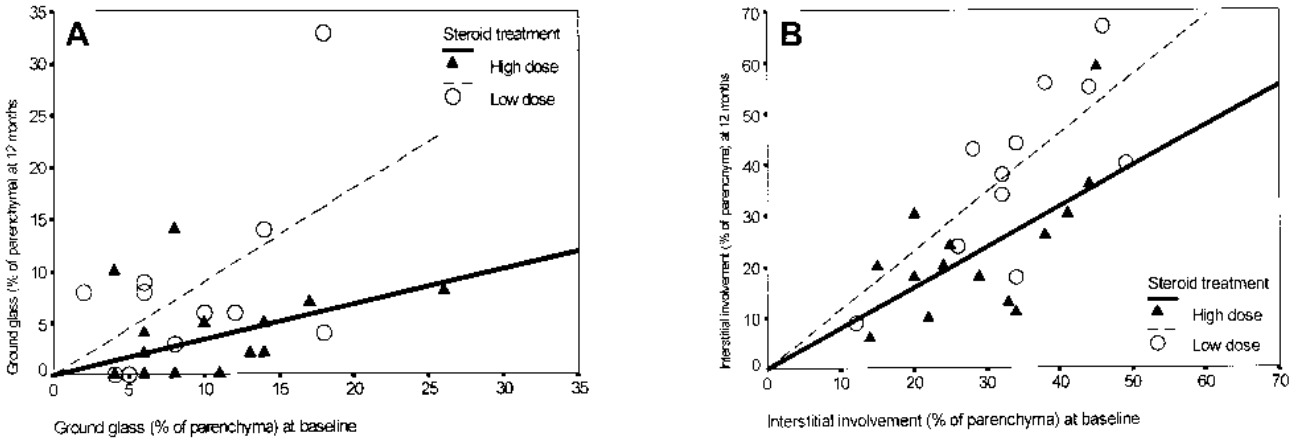

Figure 1. Ground glass score (A) and total interstitial score (B) at 12 months as a function of the respective baseline scores for patients receiving high and low dose prednisolone. Also shown are best-fit regression lines for the 2 groups.

noted only in the high dose group. This improvement was seen as early as 6 months and persisted at 12 months.

The use of high resolution CT changes as the primary endpoint for this phase I/II trial was based on recent data suggesting that CT is a sensitive[43] and reproducible[44] method for determining the morphologic extent of fibrosing alveolitis. High resolution CT scans seem to be superior to PFT in staging disease extent[45] and provide an excellent noninvasive alternative to BAL and open-lung biopsy[11,40,46]. Areas of ground glass attenuation, particularly those not associated with traction bronchiectasis or bronchiolectasis, correlate with active cellular histopathology, whereas reticular pattern corresponds to the fibrosis seen on histologic examination[40]. Ground glass appearance also corresponds to a neutrophilic alveolitis by BAL analysis[11]. These data suggest that a ground glass appearance on CT is the radiographic equivalent of inflammatory alveolitis[11], and it may be important in predicting therapeutic response and prognosis[47]. Ground glass attenuation on CT has been associated with better response to therapy[11,48,49].

In this study, the percentage of ground glass appearance as well as the composite interstitial disease score improved significantly at the end of the trial in patients receiving high doses of steroids. More than 50% of ground glass opacities regressed. In contrast, no change in the percentage of reticular involvement was noted. PFT variables in the same group (FVC, DLCO, TLC) also improved significantly between baseline and 12 months. These findings are in agreement with reports that improvement in PFT were associated with regression of the ground glass pattern[49,50]. On the other hand the patients of the low dose steroid group increased significantly in the percentage of reticular pattern compared to baseline, whereas PFT showed trends for deterioration.

Although there was no significant difference in the disease duration between the 2 groups, the significantly greater extent of reticular involvement in the low dose group was indicative of more advanced pulmonary involvement in these patients. Therefore, the lack of response in the low dose group may be related to more irreversible fibrotic disease and not necessarily to the lower doses of prednisolone. Nevertheless, the extent of ground glass involvement at baseline, which represents potentially reversible alveolitis, was similar in the 2 groups. Thus the regression of the ground glass findings in the high dose group may be seen as the synergistic effect of high dose corticosteroids and IV CP. Adjusted analyses taking into account the baseline extent of parenchymal involvement suggested that, for the same level of baseline CT involvement, the high dose group tended to have a better response than the low dose group. These analyses lend some support to the concept that high dose steroids were a key component for achieving therapeutic efficacy. However, the results should not be interpreted as showing that high dose prednisone is effective alone or better than IV pulse CP alone. Moreover, the study was not randomized and the aim was not to compare directly the differences in outcomes between the 2 groups. Patients in the low dose group were sicker and this could be a main reason for their worse outcome. Nevertheless, as a dose-finding trial, the study suggests that regimens incorporating high doses of steroids may be more likely to be beneficial and such regimens should be prioritized for testing in larger phase II/III trials. It should be emphasized that the natural history of pulmonary involvement in SSc is not well known. In that respect, stable disease under CP treatment alone may also represent a therapeutic potential, as suggested in a large study by White, *et al*[50]; therefore this regimen should also be tested in placebo controlled trials.

The treatment of SSc related ILD with immunosuppressive agents is still empiric, and most therapies have been disappointing[13-17,19]. The administration of high dose corticosteroids alone was associated with inconsistent

results[12,18,19,51]. Significant or modest improvement was noted in a minority of patients[18,19]. Cyclophosphamide is a promising agent for the treatment of SSc related ILD[19-21]. In most patients CP was given in daily oral doses. In 2 prospective open trials, the combination of oral CP with low[21] or intermediate doses of corticosteroids[20] was associated with significant improvement of FVC and static lung compliance. In a retrospective study, CP treated patients showed significantly more improvement in FVC compared with D-penicillamine, high dose prednisolone, methotrexate, or azathioprine[19].

Besides showing marginal efficacy, trials in this field have been limited in sample size. Moreover, several studies have been designed in a way that would make the interpretation of outcomes susceptible to regression-to-the-mean bias. For example, studies using low FVC as an eligibility criterion[18] may observe improvements in FVC values during followup simply due to regression-to-the mean[52,53]. One may see improvements in indices by which patients were selected[52,53], but no change in other outcomes. Along these lines, in all the studies discussed above, improvements in FVC were accompanied by a reduction or no change in the DLCO[19-21]. In contrast, the DLCO in patients in our high dose group improved significantly at 12 months. In a recent study, DLCO reflected the extent of disease on CT scans more accurately than did other functional indices[45]. Our findings of consistent patterns of improvement in DLCO, FVC, and CT scans reinforce the validity of our data regarding the beneficial effects of the high dose regimen.

Daily oral CP has been related to longterm toxicity[22,23]. Intermittent IV pulse CP treatment has been reported to be equally effective, better tolerated, and less toxic than oral daily doses[24-28]. IV pulse CP therapy of patients with IPF has given encouraging results[29,30]. Clinical data assessing the efficacy of IV pulse CP in ILD due to SSc or other collagen diseases are limited[31,32]. IV pulse CP has been given alone[31] or in combination with relatively high doses of prednisolone (50 mg/day) at the initiation of treatment with tapering over 3 weeks to 5–7.5 mg/day[32]. In one study[31], dyspnea improved substantially during therapy, but no significant improvement in FVC or on CT scans was detected. In another study[32], all patients but one, including 2 patients with SSc related ILD, showed significant functional improvement, substantial regression of ground glass opacities, and normalization of BAL findings. These conflicting results may be due to chance, concomitant use of corticosteroids in one study[32], or different populations. Patients had a predominantly reticular pattern in the first trial[31], while ground glass involvement predominated in the latter[32]. The outcomes of our patients in the low dose and high dose groups are in accord with those noted in these 2 studies, respectively.

In this study, the toxicity of intermittent IV pulse CP was not substantial. No patient withdrew because of major side effects. The coadministration of high dose prednisolone was not associated with more severe side effects during the study. Nevertheless, longterm high dose corticosteroid therapy has been related with SSc renal crisis[54], and longterm followup of patients would be essential to establish the longterm safety of these combinations. Our study group was too small to draw a reliable conclusion on this issue. Safety data are preliminary and larger scale evidence should be collected before the combination regimen can be adopted for routine use in different patients from various ethnic groups.

We found that intravenous pulse cyclophosphamide therapy was well tolerated over 12 months and combined with high doses of prednisolone showed evidence for a beneficial effect in SSc related ILD. Larger controlled randomized studies should be undertaken to elucidate the efficacy and longterm safety of the combination of IV pulse CP with high dose prednisolone in this setting, and to clarify the relative merits of the combination of these 2 regimens versus each of them alone.

REFERENCES

1. Gilliland BC. Systemic sclerosis (scleroderma). In: Isserbacher KJ, Brounwald E, Wilson JD, Martin JB, Fauci AS, Kasper IL, editors. Harrison's principles of internal medicine. 13th ed. International Edition. New York: McGraw-Hill, Inc.; 1994:1665-71.
2. Steen VD, Owens GR, Fino GJ, Rodnan GP, Medsger JA Jr. Pulmonary involvement in systemic sclerosis (scleroderma). Arthritis Rheum 1985;28:759-67.
3. Johnson DA, Drane WE, Curran J, et al. Pulmonary disease in progressive systemic sclerosis. Arch Intern Med 1989;149:589-93.
4. Manoussakis MN, Constantopoulos SH, Gharavi AE, Moutsopoulos HM. Pulmonary involvement in systemic sclerosis. Association with anti-Scl70 antibody and digital pitting. Chest 1987;92:509-13.
5. Steen VD. Epidemiology of rheumatic disease. Systemic sclerosis. Rheum Dis Clin North Am 1990;16:641-54.
6. Lee P, Langevitz P, Alderdize CA, et al. Mortality in systemic sclerosis (scleroderma). Q J Med 1992;298:139-48.
7. Steen VD, Costantino JP, Shapiro AP, Medsger JA Jr. Outcome of renal crisis in systemic sclerosis: relation to availability of angiotensin converting enzyme inhibitors. Ann Intern Med 1990;113:352-7.
8. Rossi GA, Bitterman PB, Rennard SI, Serrans VJ, Crystal RG. Evidence for chronic inflammation as a component of the interstitial lung disease associated with progressive systemic sclerosis. Am Rev Respir Dis 1985;131:612-7.
9. Lynch JP III, McCune WJ. Immunosuppressive and cytotoxic pharmacotherapy for pulmonary disorders. Am J Respir Crit Care Med 1997;155:395-420.
10. Harrison NK, Glanville AR, Strickland B, et al. Pulmonary involvement in systemic sclerosis: the detection of early changes by thin section CT scan, bronchoalveolar lavage and ^{99m}Tc-DTPA clearance. Respir Med 1989;83:403-14.
11. Warrick JH, Bhalla M, Schabel SI, Silver RM. High resolution computed tomography in early scleroderma lung disease. J Rheumatol 1991;18:1520-8.
12. Silver RM, Miller KS, Kinsella MB, Smith EA, Schabel ST. Evaluation and management of scleroderma lung disease using bronchoalveolar lavage. Am J Med 1990;88:470-6.
13. Steen V, Owens G, Redmond C, Rodnan GP, Medsger JA Jr. The effect of D-penicillamine on pulmonary findings in systemic

sclerosis. Arthritis Rheum 1985;28:882-8.
14. de Clerk LS, Dequeker J, Francx L, Demedts M. D-penicillamine therapy and interstitial lung diseases in scleroderma. A long-term follow-up study. Arthritis Rheum 1987;30:643-50.
15. Furst DE, Clements PJ, Hillis S, et al. Immunosuppression with chlorambucil versus placebo, for scleroderma. Results of a three-year parallel, randomized, double-blind trial. Arthritis Rheum 1989;32:584-93.
16. Gruber BL, Kaufman LD. A double-blind randomized controlled trial of ketotifen versus placebo in early diffuse scleroderma. Arthritis Rheum 1991;34:362-6.
17. Ferri C, Bernini L, Bombardieri S, Pasero G. Long-term griseofulvin treatment for progressive systemic sclerosis. Scand J Rheumatol 1986;15:356-62.
18. Behr J, Vogelmeier C, Beinert T, et al. Bronchoalveolar lavage for evolution and management of scleroderma disease of the lung. Am J Respir Crit Care Med 1996;154:400-6.
19. Steen VD, Lanz JK Jr, Conte C, Owens GR, Medsger JA Jr. Therapy for severe interstitial lung disease in systemic sclerosis: a retrospective study. Arthritis Rheum 1994;37:1290-6.
20. Akesson A, Scheja A, Lundin A, Wollheim FA. Improved pulmonary function in systemic sclerosis after treatment with cyclophosphamide. Arthritis Rheum 1994;37:729-35.
21. Silver RM, Warrick JH, Kinsella MB, Staudt LS, Baumann MH, Strange C. Cyclophosphamide and low-dose prednisone therapy in patients with systemic sclerosis (scleroderma) with interstitial lung disease. J Rheumatol 1993;20:838-44.
22. Decker JL. Toxicity of immunosuppressive drugs in man. Arthritis Rheum 1973;16:89-91.
23. Schein PS, Winokur SH. Immunosuppressive and cytotoxic chemotherapy: long term complications. Ann Intern Med 1975;82:84-95.
24. Cupps TR. Cyclosphosphamide: to pulse or not to pulse? Am J Med 1990;89:399-402.
25. Austin HA, Klippel JH, Balow JE, et al. Therapy of lupus nephritis. Controlled trial of prednisone and cytotoxic drugs. N Engl J Med 1986;314:614-9.
26. Boumpas DT, Barez S, Klippel JH, Balow JE. Intermittent cyclophosphamide for the treatment of autoimmune thrombocytopenia in systemic lupus erythematosus. Ann Intern Med 1990;112:674-7.
27. Leroy JP, Drosos AA, Yiannopoulos DI, Youinou P, Moutsopoulos HM. Intravenous pulse cyclophosphamide therapy in myositis and Sjögren's syndrome. Arthritis Rheum 1990;33:1579-81.
28. Fort JG, Abrazo JL. Reversal of progressive necrotizing vasculitis with intravenous pulse cyclophosphamide and methylprednisolone. Arthritis Rheum 1988;31:1194-8.
29. Baughman RP, Lower EE. Use of intermittent intravenous cyclophosphamide for idiopathic pulmonary fibrosis. Chest 1992;102:1090-4.
30. Kolb M, Kirschner J, Riedel W, Wirtz H, Schmidt M. Cyclophosphamide pulse therapy in idiopathic pulmonary fibrosis. Eur Respir J 1998;12:1409-14.
31. Vorai G, Earle L, Jimenez SA, Steinez RM, Varga J. A pilot study of intermittent intravenous cyclophosphamide for the treatment of systemic sclerosis associated lung disease. J Rheumatol 1998; 25:1325-9.
32. Schnabel A, Reutec M, Gross WL. Intravenous pulse cyclophosphamide in the treatment of intersitial lung disease due to collagen vascular diseases. Arthritis Rheum 1998;41:1215-20.
33. Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis. Arthritis Rheum 1980;23:581-90.
34. Leroy EC, Black C, Fleischmajer R, et al. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol 1988;15:202-5.
35. Watters LC, Schwarz MI, Cherniack RM, et al. Idiopathic pulmonary fibrosis: pretreatment bronchoalveolar lavage cellular constituents and their relationship with lung histopathology and clinical response to therapy. Am Rev Respir Dis 1987;135:696-704.
36. Pakas I, Vlachoyiannopoulos PG, Skopouli FN, Moutsopoulos HM. Intravenous pulses of cyclophosphamide for scleroderma interstitial lung disease [abstract]. Clin Exp Rheumatol 1998;16:375.
37. Brennan P, Silman A, Black C, et al. Reliability of skin involvement measures in scleroderma. Br J Rheumatol 1992;31:457-60.
38. Knudson RJ, Statin RC, Lebowitz MD, Burrows B. The maximal expiratory flow volume curve. Normal standards, variability and effects of age. Am Rev Respir Dis 1976;11:587-600.
39. Wells AU, Hansell DM, Corrin B, et al. High resolution computed tomography as a predictor of lung histology in systemic sclerosis. Thorax 1992;47:738-42.
40. Remy-Jardin M, Giraud F, Remy J, Copin MC, Gosselin B, Duhamel A. Importance of ground-glass attenuation in chronic diffuse infiltrative lung disease: Pathologic-CT correlation. Radiology 1993;189:693-8.
41. Wells AU, Hansell DM, Rubens MB, Cullinan P, Black CM, duBois RM. The predictive value of appearances on thin-section computed tomography in fibrosing alveolitis. Am Rev Respir Dis 1993;148:1076-83.
42. Greenwald GI, Tashkin DP, Gong H, et al. Longitudinal changes in lung function and respiratory symptoms in progressive systemic sclerosis. Prospective study. Am J Med 1987;83:83-91.
43. Schurawitzki H, Stiglbauer R, Graninger W, et al. Interstitial lung disease in progressive systemic sclerosis: high resolution CT versus radiography. Radiology 1990;176:755-9.
44. Collins CD, Wells AU, Hansell DM, et al. Observer variation in pattern type and extent of disease in fibrosing alveolitis on thin section computed tomography and chest radiography. Clin Radiol 1994;49:236-40.
45. Wells AU, Hansell DM, Rubens MB, et al. Fibrosing alveolitis in systemic sclerosis. Indices of lung function in relation to extent of disease on computed tomography. Arthritis Rheum 1997; 40:1229-36.
46. Dansin E, Wallaert B, Remy-Jardin M, et al. Study of high-resolution thoracic computerized tomography and bronchoalveolar lavage in 36 patients presenting with systemic disease and a normal thoracic radiography. Rev Mal Respir 1996;8:551-8.
47. Gay SE, Kazerooni EA, Toews GB, et al. Idiopathic pulmonary fibrosis. Predicting response to therapy and survival. Am J Respir Crit Care Med 1998;157:1063-72.
48. Terriff B, Kwan S, Chan-Yeung M, Muller HL. Fibrosing alveolitis: Chest radiography and CT as predictors of clinical and functional impairment at follow-up in 26 patients. Radiology 1992;184:445-9.
49. Wells AU, Rubens MB, duBois RM, Hansell DM. Serial CT in fibrosing alveolitis: prognostic significance of the initial pattern. Am J Roentgenol 1993;161:1159-65.
50. White B, Moore WC, Wigley FM, Xio HQ, Wise RA. Cyclophosphamide is associated with pulmonary function and survival benefit in patients with scleroderma and alveolitis. Ann Intern Med 2000;132:947-54.
51. Kallenberg CGM, Jansen HM, Elema JD. The steroid-responsive interstitial pulmonary disease in systemic sclerosis: monitoring by bronchoalveolar lavage. Chest 1984;86:489-92.
52. Yudkin PL, Stratton IM. How to deal with regression to the mean in intervention studies. Lancet 1996;347:241-3.
53. Ioannidis JPA, Karassa FB. Bias in uncontrolled therapeutic trials in rheumatology due to selection of populations with extreme characteristics. J Rheumatol 2001;28:1881-7.
54. Helfrich DJ, Banner B, Steen VD, Medsger JA Jr. Normotensive renal failure in systemic sclerosis. Arthritis Rheum 1989; 32:1128-34.