

# Cyclophosphamide Pulse Therapy in the Treatment of Systemic Sclerosis Associated Interstitial Lung Disease: An Observational Study

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## ABSTRACT

**Introduction:** Scleroderma is a multisystem autoimmune connective tissue disease with approximately 90% of patients having lung involvement. It is the leading cause of morbidity and mortality in scleroderma. There is no effective treatment once there is lung involvement in the form of fibrosis.

**Study setting:** Conducted in a tertiary care center between January 2017 and December 2019.

**Aim:** To evaluate the efficacy of intravenous cyclophosphamide in patients with scleroderma-associated interstitial lung disease (ILD).

**Study population:** Symptomatic patient with scleroderma with high-resolution computed tomography (HRCT)-proven non-specific interstitial pneumonia (NSIP)-pattern ILD.

**Methodology:** Patients received 12 cycles of cyclophosphamide at a dose of 10 mg/kg every 4 weeks. Patients were followed up for 1 year after treatment completion. A six-minute walk test (6MWT) and spirometry were done at baseline and then every 6 months up to 2 years. Diffusing capacity of lung for carbon monoxide (DLCO) was done at baseline and then yearly for up to 2 years.

**Results:** A total of 38 patients completed the study. The majority of patients had diffuse cutaneous type of systemic sclerosis. Throughout the study period, there was a gradual worsening of dyspnea as measured by the Modified Medical Research Council (mMRC) scale. Mean forced vital capacity (FVC) improved with 1 year of treatment, but later steadily decreased during follow-up. Similarly, DLCO also improved during 1-year treatment, but the improvement was not sustained during follow-up. There was a statistically significant improvement in 6MWD at the end of 6 months. This was followed by a gradual fall in 6MWD during follow-up. The only adverse event noted was persistent leukopenia in one patient.

**Conclusion:** Intravenous pulse cyclophosphamide therapy in patients with scleroderma-associated ILD is associated with stabilization of pulmonary function during the treatment period, but not maintained during follow-up.

**Keywords:** Cyclophosphamide, Interstitial lung disease, Scleroderma.

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## ABBREVIATIONS USED IN THIS ARTICLE

HRCT = High-resolution computed tomography; NSIP = Non-specific interstitial pneumonia; 6MWT = Six-minute walk test; DLCO = Diffusing capacity of lung for carbon monoxide; mMRC = Modified Medical Research Council; FVC = Forced vital capacity; CT = Computed tomography; ACR-EULAR = American college of Rheumatology-european league against rheumatism; CBC = Complete blood count; ANOVA = One-way analysis of variance; SPSS = Statistical package for the social sciences (SPSS); US FDA = US Food and drug administration; RNP = Ribonucleoprotein; SSA = Sjogren syndrome antibody; UIP = Usual interstitial pneumonia.

## INTRODUCTION

Scleroderma (systemic sclerosis) is a multisystem autoimmune connective tissue disease affecting the skin and visceral organs such as the lungs, kidney, heart, and gastrointestinal tract. It is characterized by microvascular injury and excessive fibrosis of the skin and viscera. Approximately 90% of patients will eventually have lung involvement, and ILD is the leading cause of morbidity and mortality in systemic sclerosis.<sup>1</sup> Among patients with scleroderma, those with positive anti-Scl-70 antibodies are more prone to develop ILD whereas those with positive anticentromere antibodies are

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more prone to develop pulmonary hypertension.<sup>2</sup> The mortality rate among patients with severe restrictive lung disease due to scleroderma, is approximately 42% within 10 years after disease onset.<sup>3</sup> Among ILD, NSIP is the most frequently encountered pattern.



## Statistical Methods

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented as mean  $\pm$  SD (minimum–maximum) and results on categorical measurements are presented in numbers (%). Significance is assessed at a 5% level of significance.

One-way analysis of variance (ANOVA) followed by the Bonferroni *post hoc* test for pairwise comparison was done to compare baseline values with the post values.

Chi-squared and Fisher's exact tests have been used to find the significance of study parameters on a categorical scale between two or more groups, a non-parametric setting for qualitative data analysis.

## Statistical Software

The statistical software, namely, statistical package for the social sciences (SPSS), version 18.0, and R environment version 3.2.2 were used for the analysis of the data, and Microsoft Word and Microsoft Excel have been used to generate graphs, tables, etc.

## RESULTS

A total of 40 patients were enrolled in the study. Patients who had received less than 12 cycles of cyclophosphamide were not taken for statistical analysis. One patient had to discontinue treatment because of a persistently low WBC count. One patient did not complete 12 cycles of cyclophosphamide as the patient was lost to follow-up. So, finally, 38 patients were available for statistical analysis (Table 2).

The mean age of the study population was  $45.79 \pm 11.78$ . The majority of the patients (89.5%) were females.

Most of the patients belonged to the diffuse cutaneous systemic sclerosis type (Table 3).

Throughout the study period, there was a gradual worsening of dyspnea as measured by the mMRC scale (Fig. 1).

The FVC values recorded at baseline and every 6 months during therapy and up to 1 year after the withdrawal of therapy were compared (Table 4).

The mean FVC (% predicted) at baseline was  $57.31 \pm 10.06$ . There were three patients who had FVC below 45% at the baseline.

The mean FVC and percentage change in FVC increased after 1 year of treatment with monthly intravenous cyclophosphamide;

**Table 2:** Antibody distribution of patients

Antibody	Number of patients	%
Anti-Scl-70	19	50.0
RNP	7	18.4
Anti-centromere	3	7.9
SSA	1	2.6
None	2	5.3
Others	6	15.8
Total	38	100.0

RNP, Ribonucleoprotein; SSA, sjogren syndrome antibody

**Table 3:** Type of disease in study patients

Type	Number of patients	%
Diffuse	35	92.1
Limited	3	7.9
Total	38	100.0

however, the improvement was not statistically significant ( $p = 0.485$ ). Individually, 20 out of the 38 patients showed improvement or stabilization on spirometry. Only three patients had a fall in FVC above 10% from baseline after 1 year of treatment.

Out of 3 patients who had very low FVC (below 45%) at baseline, 2 showed improvement with therapy after 1 year.

On further follow-up of the study patients for 1 year after completion of the treatment, the mean FVC was found to be steadily decreasing (Figs 2 and 3).

The DLCO was assessed at baseline, at 12 months, and at 24 months (Table 5).

Similar to FVC values, the DLCO also showed improvement after 1 year of therapy though not statistically significant. The improvement in DLCO was not sustained 1 year after the completion of treatment (Fig. 4).

Six-minute walk test was done at baseline and then at 6, 12, 18, and 24 months (Table 6).

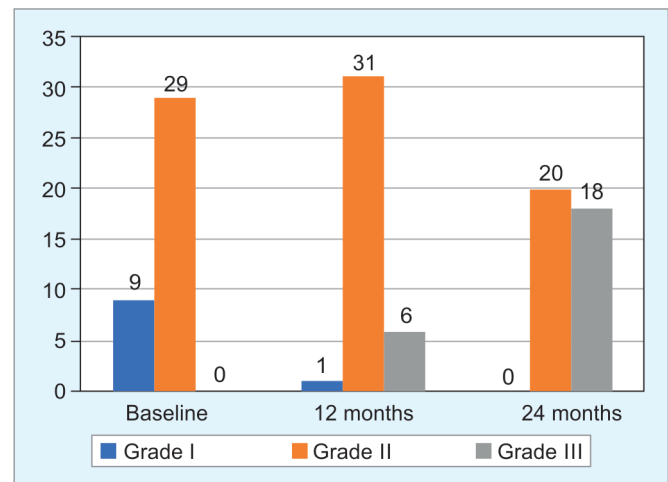
Six-minute walk distance (6MWD) increased from baseline after treatment. There was a statistically significant improvement in 6-minute walk distance at the end of 6 months of treatment. Even though there was a gradual decline in 6MWD after 1 year of treatment, it was not statistically significant (Fig. 5).

The only adverse event noted in this study was persistent leukopenia in 1 patient and that patient had to discontinue cyclophosphamide therapy.

## DISCUSSION

Systemic sclerosis-related ILD causes significant morbidity and mortality. Even though cyclophosphamide has been the cornerstone of treatment for a long time, the optimal treatment for this condition still remains uncertain. This prospective observational study evaluated the effect of cyclophosphamide on scleroderma-related ILD. Spirometry, DLCO, and 6MWT were used in this study to assess the response of ILD to treatment with cyclophosphamide.

This study showed a significant but modest improvement in FVC and 6MWD in patients treated with cyclophosphamide over a period of 1 year, but this improvement in FVC was not maintained during the 1-year follow-up period. Gas transfer as measured by DLCO also showed improvement during the treatment period, but it was also not maintained during 1-year follow-up period. The only parameter which showed worsening throughout the

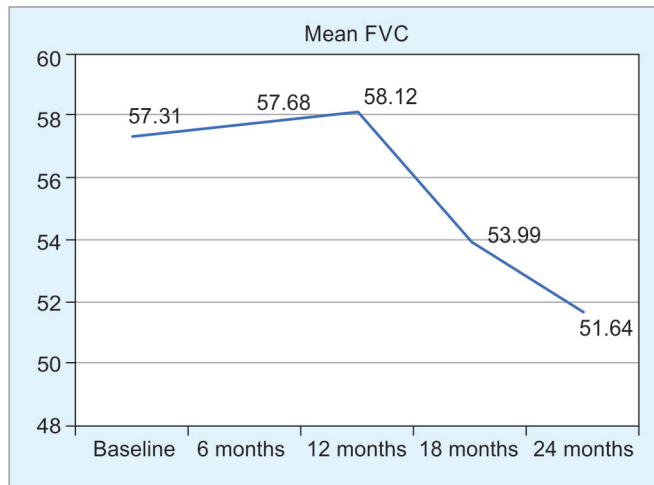
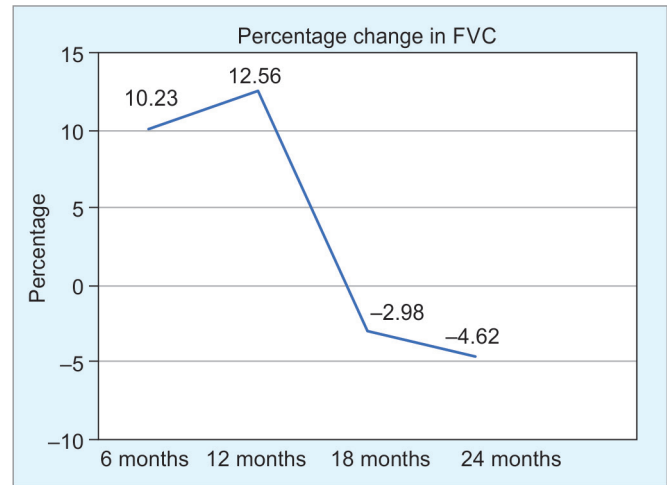


**Fig. 1:** Change in dyspnea over 24 months – mMRC grading

**Table 4:** Serial assessment of FVC during study period

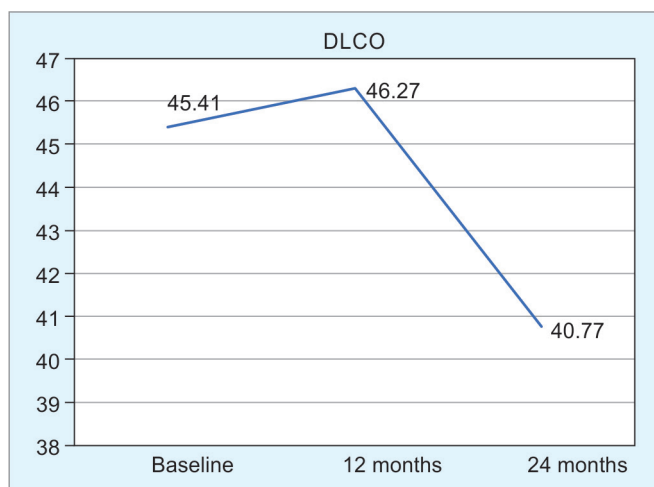
FVC	Minimum–Maximum	Mean $\pm$ SD	Difference	t-value	p-value
Baseline	38.00–80.00	57.31 $\pm$ 10.06	–	–	–
6 months	33.00–78.00	57.68 $\pm$ 10.58	0.376	0.330	0.743
12 months	35.00–76.00	58.12 $\pm$ 10.14	0.37	0.705	0.485
18 months	34.00–77.00	53.99 $\pm$ 11.05	3.313	2.353	0.024*
24 months	31.50–74.00	51.64 $\pm$ 10.85	5.669	3.893	<0.001**

\*Significant; \*\*Very significant

**Fig. 2:** Change in FVC during study period**Fig. 3:** Percentage change in FVC during the study period**Table 5:** The DLCO assessment in different study periods

DLCO	Minimum–Maximum	Mean $\pm$ SD	Difference	t-value	p-value
Baseline	30.00–63.10	45.41 $\pm$ 11.25	–	–	–
1 year	28.00–68.10	46.27 $\pm$ 10.56	0.37	0.991	0.328
2 years	25.80–65.00	40.77 $\pm$ 9.86	4.639	3.411	0.002**

\*Significant; \*\*Very significant

**Fig. 4:** Change in DLCO over the study period

study period was dyspnea. In a study where scleroderma-related ILD patients were followed up for 2 years after treatment with cyclophosphamide for 1 year, it was found that the beneficial effects of cyclophosphamide on pulmonary function and health status continued up to 18 months, but was no longer apparent at 24 months.<sup>8</sup> As the effect of cyclophosphamide is not maintained after stopping treatment, usually maintenance therapy is advisable. The optimal choice for this purpose is not known. Observational studies support the use of mycophenolate mofetil or azathioprine as maintenance agents. However, the optimal duration of maintenance therapy is also not known.

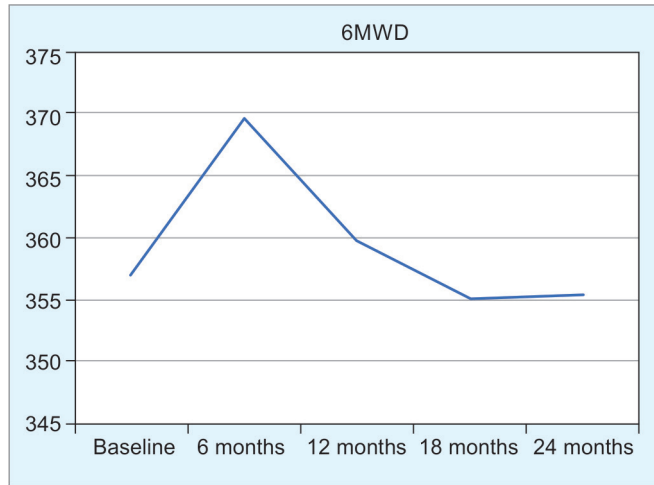
The ACR-EULAR guidelines of 2017 recommend cyclophosphamide as the first choice of therapy for scleroderma related ILD, especially for those patients with progressive ILD.<sup>9</sup>

In an observational study of 6 months of pulse cyclophosphamide, there was a significant improvement in FVC and 6MWD at 12-month follow-up in patients with scleroderma-associated ILD.<sup>10</sup>

**Table 6:** The 6MWD serial follow-up values

MWD	Minimum–Maximum	Mean $\pm$ SD	Difference	t-value	p-value
0	240.00–465.00	356.92 $\pm$ 53.53	–	–	–
6 months	270.00–495.00	369.61 $\pm$ 54.64	12.684	2.745	0.009**
12 months	290.00–480.00	359.74 $\pm$ 47.67	2.816	0.508	0.614
18 months	300.00–460.00	355.13 $\pm$ 44.95	1.789	0.316	0.754
24 months	280.00–465.00	355.39 $\pm$ 46.85	1.526	0.297	0.768

\*Significant; \*\*Very significant



**Fig. 5:** Change in 6MWD over the study period

Recent studies including scleroderma lung study II showed a comparable efficacy for cyclophosphamide and mycophenolate mofetil, but with lesser toxicity with mycophenolate. However, these comparative studies were with oral cyclophosphamide which has a higher cumulative dose compared to pulse cyclophosphamide more adverse events. Intravenous cyclophosphamide is safer and compared with mycophenolate is cheaper and has similar efficacy.<sup>11</sup> In a review article by Vonk, it is suggested that a randomized controlled trial needs to be conducted to compare intravenous pulse cyclophosphamide and mycophenolate mofetil in scleroderma related ILD.<sup>12</sup>

Recently, other drugs that are undergoing trial for scleroderma-related ILD include pirfenidone and nintedanib. In the scleroderma lung study III, pirfenidone is combined with mycophenolate mofetil, and its efficacy is being investigated. In the phase II LOTUSS clinical trial of pirfenidone, in scleroderma-related ILD, the adverse events were similar to those seen in patients on pirfenidone for IPF.<sup>13</sup>

Another antifibrotic drug that was tried in scleroderma-related ILD is nintedanib. In the study by Distler et al., patients on nintedanib were found to have a lower rate of decline in FVC compared to placebo. The adverse event profile was found to be similar to those seen in patients with IPF.<sup>14</sup>

Nintedanib is the only drug approved by US Food and Drug Administration (US FDA) to treat scleroderma-related ILD. However, it is a very expensive drug. In the scleroderma lung study II, even though both oral cyclophosphamide and mycophenolate mofetil were found to be equally effective, adverse events were less for mycophenolate. However, mycophenolate is expensive compared

to cyclophosphamide. In this study, adverse events were minimal. In most of the studies where there were significant adverse events to cyclophosphamide, it was given in the oral form. Monthly pulse cyclophosphamide is associated with fewer adverse events compared to oral cyclophosphamide.

**Adverse events:** The only adverse event noted in this study was the development of persistent leucopenia in one patient. The reduced incidence of adverse events in this study may be due to the lower dose of cyclophosphamide used. All the previous studies also demonstrated that intravenous pulse cyclophosphamide therapy was associated with lower adverse events compared to oral cyclophosphamide.<sup>15,16</sup> It is also possible that proper hydration of the patient during the pulse therapy reduced adverse events.

Another significant adverse event reported in previous studies is an increased incidence of malignancy in patients treated with cyclophosphamide.<sup>17,18</sup> The patients were followed up only for 2 years from the beginning of the study and none of the patients developed malignancy. These patients should be followed up for a longer period to assess the risk of malignancy.

### Limitations

The small sample size and short duration of follow-up are the main limitations. Other problems are a lower dose compared to other trials and the non-uniformity of the sample. The HRCT thorax was not repeated in all patients to assess treatment response. This may affect the treatment response and the sample size is small to consider multivariate analysis.

### CONCLUSION

Intravenous pulse cyclophosphamide therapy in patients with scleroderma-associated ILD is associated with stabilization of pulmonary function during the treatment period. However, this stabilization is not maintained during the follow-up period after treatment. A gradual decline in lung function is seen during the follow-up. So, these patients may need either treatment with other agents like mycophenolate mofetil or further intermittent pulsing with cyclophosphamide. Another significant observation of the study was that pulse therapy with cyclophosphamide is not associated with any significant adverse events if proper precautions are taken. However, caution is still warranted as the long-term effects of cyclophosphamide were not assessed.

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