Original Article

Effect of Sequential Intravenous Pulse Cyclophosphamide-Azathioprine in Systemic Sclerosis-Interstitial Lung Disease: An Open-Label Study

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Abstract

Background. Systemic sclerosis (SSc) is a rare connective tissue disorder of unknown aetiology. Pulmonary involvement contributes substantially to its morbidity and mortality. Treatment of pulmonary disease due to SSc remains unsatisfactory. We examined the effect of sequential six-month intravenous pulse therapy with cyclophosphamide (CYC) followed by azathioprine and low-dose corticosteroids on SSc associated interstitial lung disease (SSc-ILD).

Methods. In a single-centre, prospective, observational, open-labelled study; nine patients (eight females, one male) with SSc-ILD were treated with intravenous pulse CYC ($600mg/m^2$ body surface area) at monthly interval for six cycles with oral prednisolone 10mg daily. Subsequently, azathioprine (2-3mg/Kg) was administered while continuing with the same dose of prednisolone. Primary end-points were forced vital capacity (FVC) and high resolution computed tomography (HRCT) scan of thorax score. Secondary end-points were quality of life measured by health assessment questionnaire-disability index (HAQ-DI) and six-minute walk distance (6WMD) test.

Results. After one year of observation, the FVC showed significant improvement (p=0.003). The 6WMD also improved significantly (p=0.0028). However, change in HRCT scan scoring and HAQ-DI score was not significant.

Conclusions. Intravenous, pulse CYC followed by azathioprine along with low-dose corticosteroids produces significant improvement in FVC and 6WMD at 12-month follow-up without significant change in radiological manifestations and health status. [Indian J Chest Dis Allied Sci 2016;58:7-10]

Key words: Cyclophosphamide, Interstitial lung disease, Systemic sclerosis, Scleroderma.

Introduction

Systemic sclerosis (SSc) is a rare connective tissue disorder of unknown aetiology characterised by obliterative microvasculopathy,[1] with involvement of lungs, skin, heart, kidneys and the gastrointestinal tract. Pulmonary involvement may be found in up to 80% of patients with SSc. Interstitial lung diseases (ILDs) and pulmonary arterial hypertension (PAH) are two common causes of death in these patients.

In patients with SSc, 40% of the patients will develop moderate restrictive ventilatory impairment and upto 15% will develop severe restrictive ILD (forced vital capacity [FVC] <50% predicted). The 10-year survival rate is approximately 40% to 50% in these patients.[2,3] A rapid decline in lung function occurs in the initial four years of the disease. The patients at risk of ILD progression should be identified and aggressive treatment be started early in an attempt to stop disease progression.

Immunosuppression has been proposed a useful treatment for SSc-ILD to achieve and maintain remission. D-penicillamine, prednisolone, relaxin, methotrexate, interferon (IFN)-gamma and cyclophosphamide (CYC) have been used for the treatment of SSc-ILD, mostly with disappointing results and only CYC has been shown to slow down the loss of FVC in some patients.[4,5] The present study was carried out with an objective to evaluate the effect of sequential six-month intravenous pulse CYC therapy followed by azathioprine alongwith low-dose corticosteroids on SSc-ILD.

Material and Methods

This was a single-centre, prospective, open-label, observational study carried out in the Department of Pulmonary Medicine, R.G. Kar Medical College and Hospital, Kolkata, from January 2012 to December 2013 after approval by the Institutional Ethical Committee. Written informed consent was obtained from all the patients.

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Patients with SSc were enrolled in the study if they met the following criteria: (i) onset of their first non-Raynaud's manifestation within the last five years; (ii) FVC >30% and <85% of predicted, exertional dyspnoea $\geq$Grade 1 according to the modified Medical Research Council (mMRC) scale; (iii) evidence of active alveolitis defined by the presence of any ground-glass opacity on thoracic high resolution computed tomography (HRCT) images, irrespective of the additional presence of fibrosis or honey-combing.

The patients were excluded from the study if: (i) the forced expiratory volume of the lung during the first second (FEV_1)/FVC ratio was <70%; (ii) smoking history within the past six months; (iii) significant lung pathology other than ILD; (iv) significant PAH (pulmonary artery systolic pressure >40mmHg as evidenced by 2D echocardiography with Doppler study); (v) unexplained haematuria (>10 RBC/HPF), serum creatinine >1.5mg/dL, haematologic abnormalities (<4000 WBC/mm³, <150,000 platelets/mm³); (vi) pregnancy or unwillingness to utilise appropriate contraceptive measures (urinary pregnancy tests were done at the onset of treatment); (vii) serious concomitant medical illness like active tuberculosis; (viii) previous treatment with oral CYC for more than four weeks or intravenous CYC for $\geq$2 doses, or recent use of other potentially disease-modifying medications (azathioprine, methotrexate, D-penicillamine, etc.) and patients taking prednisolone more than 10mg daily.

The patient were treated with six-month intravenous pulse CYC 600mg/m³ body surface area, once a month therapy, followed by azathioprine along with low-dose corticosteroids (prednisolone 10mg daily) for one year. The patients were properly monitored for adverse effects with monthly examination of complete haemogram and renal function test for initial six months and complete haemogram and liver function test for the next six months. The outcome was evaluated using the following measures: (i) FVC measured by spirometry, performed as per standard protocol[6]; (ii) parenchymal involvement as evidenced on HRCT scan of thorax; (iii) 6WMD measured by six minute walk test as per standard protocol[7]; and (iv) quality of life as measured by health assessment questionnaire-disability index (HAQ-DI)[8].

The FVC (%predicted) and 6WMD test were repeated at three months, six months and 12 months. Improvement was defined as a 10% increase in FVC (%predicted), and deterioration was defined as 10% decline of FVC (%predicted). Patients who did not demonstrate improvement or deterioration were considered with stable disease. The HRCT scan, quality of life assessment by HAQ-DI was repeated at the end of 12-month follow-up period.

The following investigations were carried out in all patients: blood for complete haemogram, urea, creatinine, liver function test, urine examination, rheumatoid factor (RA), antinuclear antibodies (ANA) (by Hep 2 method), Anti-Scl70 and centromere antibodies.

The HRCT scans were scored by two independent radiologists who were blinded to the treatment protocol for the extent of parenchymal abnormality in each of three lung zones: upper (lung apex to aortic arch), middle (aortic arch to inferior pulmonary veins), lower (inferior pulmonary veins to diaphragm). The CT abnormalities were recorded in four categories on a Likert scale (0=absent, 1=1%-25%, 2=26%-50%, 3=51%-75% and 4=76%-100%). Scoring was done for isolated ground-glass opacity, opacity in the absence of reticular opacity or architectural distortion), lung fibrosis (reticular opacification, traction bronchiectasis), and honey-combing (clustered air-filled cysts with dense walls) in each of the three zones and a total score was obtained by the addition of all scores.[9]

Statistical Analysis

The data were collected by authors and statistical analysis were done using Statistical Package for the Social Sciences (SPSS) (IBM software, Microsoft excel and graphpad software packages).

Results

We identified 11 patients of pulmonary SSc-ILD during the study period. Among them nine patients were eligible for the study. Two patients were excluded from the study; one because of concomitant tubercular lymphadenitis and another patient, a 16-year-old female who refused to participate in the study due to concerns of fertility-related adverse effects from CYC.

The demographic and clinical characteristics of the patients are shown in tables 1 and 2.

Five patients showed an improvement in FVC, while four remained stable. Eight patients showed improvement in 6WMD test, while one showed a worsening. The

Table 1. Demographic characteristics of patients.

Characteristics	Results
Sex	8 Female, 1 Male
Diffuse scleroderma (% of patients)	All
Anti Scl 70 positive	All
Age	35.5±9.4*

*=Mean expressed as mean ± standard deviation

Table 2. Clinical characteristics of the patients.

Parameter	Baseline (Mean±SD)	12 months (Mean±SD)	p-Value
FVC (%pred)	53.77±10.32	61.89±10.093	0.003
6 MWD	328.89±53.43	455.22±115.09	0.0028
HRCT score	9.88±3.178	9±3.9	0.28
HAQ-DI	0.59±0.287	0.291± 0.353	0.053

Definition of abbreviations: SD=Standard deviation; FVC (%pred)=Forced vital capacity (%predicted); 6MWD=6 minute walk distance; HAQ-DI=Health assessment questionnaire-disability index.

HRCT score showed improvement in five, stability in three and worsening in one patient.

The FVC and the 6WMD showed significant improvements (p=0.003 and p=0.0028, respectively) while the HRCT and HAQ-DI score did not show any significant improvement (p>0.05).

None of the nine patients had any severe adverse events related to CYC use that necessitated cessation of the drug. Three patients complained of nausea, two had alopecia, two suffered from upper respiratory tract infections that resolved with antibiotics. Two patients suffered from anaemia.

Discussion

In this open-label study, we prospectively evaluated the effects of sequential six-month intravenous pulse CYC therapy followed by azathioprine along with low-dose corticosteroids in SSc-ILD patients. It demonstrated modest but significant improvement in FVC and 6WMD after one year. However, HAQ-DI and radiological change on HRCT chest did not show significant improvement at 12 months.

Although various immunosuppressive agents have been tried for SSc-ILD, we used sequential CYC and azathioprine. The former drug has the most robust quality of evidence regarding its efficacy for this condition. We limited CYC therapy to six months because of concerns over potential toxicity with long-term drug administration. In particular, long-term adverse events, including infertility, cumulative bone marrow toxicity, and carcinogenic potential are dose-dependent. In regimens using intravenous pulse therapy much smaller cumulative doses of CYC are used, potentially reducing toxicity as compared to oral CYC. We also added low doses of prednisolone (10mg/day) in order to reduce the risk of scleroderma renal crisis. Several uncontrolled studies have shown that intravenous CYC for six months (at dosages ranging around 0.7-1.5 g per month) can reduce the percentage of neutrophils in the bronchoalveolar lavage (BAL)[10] and can improve pulmonary functions in some SSc associated ILD patients.[10,11,14-17] In most studies this improvement was not statistically significant, probably due to the small number of patients evaluated and heterogeneity of response. However, pooled data analysis from three studies that evaluated a total of 53 patients with SSc treated this way, showed improvement in lung function. In the present study too six-month intravenous pulse CYC therapy followed by azathioprine along with low-dose corticosteroids in SSc-ILD patients produced a small, but significant improvement in FVC.[11] Since lung functions have been suggested as the most important prognostic factors for lung disease and survival of patients with SSc,[12,13] these observations support the use of CYC for the treatment of these patients. However, the optimum duration of treatment remains to be established.

The long-term follow-up data of patients treated with intravenous CYC for six months suggest that after treatment has stopped deterioration occurs in some patients, sometimes at a significant rate.[14] Prolonging treatment for 12 months, may lead to further improvement.[15,16] Although best schedule is still undetermined, we modified the system based on vasculitis treatment protocols, adding azathioprine for the next six months.

In the present study, we observed regression of ground-glass opacities in HRCT scan of thorax repeated after 12 months follow-up but the fibrosis score did not show significant improvement. Similar observations were reported in the study by Davas et al.[15] We found significant improvement in 6WMD between baseline and 12 months. We measured both the oxygen desaturation and distance covered during the 6WMD. In the study by Villalba et al[18] desaturation during 6WMD test along with the walk distance was found to be useful in predicting the severity of SSc-ILD.

The improvement of the HAQ-DI score in our patients did not reach statistical significance possibly because of the small sample size. A multi-centre, double-blind, randomised, placebo-controlled trial (Scleroderma Lung Study)[19] evaluated the effects of oral CYC on FVC and health-related symptoms in 158 patients of SSc with evidence of active alveolitis. This study showed significant improvement in FVC as well as HAQ-DI score.

The greatest benefit was seen in patients with more fibrotic lung disease on HRCT scan.[20] When patients were evaluated after one year of stopping therapy (24 months) into the trial, benefits accrued to 18 months and then waned to placebo levels with the exception of the improvement in dyspnoea.[19] Another trial, Fibrosing Alveolitis in Scleroderma Trial (FAST)[19] included 45 patients with SSc-associated ILD who were randomised to receive prednisolone (20mg/day) and six CYC infusions (600mg/m² monthly) or placebo. It showed improvement in FVC, with a trend towards statistical significance (p=0.08) but no improvement in secondary outcome measures.

The present study has several limitations. We did not evaluate the change in pulmonary artery pressure after treatment. Using transthoracic Doppler echocardiography to screen scleroderma patients, the prevalence of pulmonary hypertension has been reported to range from 13% to 35%.[22] Diffusion capacity measurements were not obtained. This would have provided information about the impact of treatment on gas exchange. Finally, the small sample size and open-labelled nature of the study precludes definitive conclusions on the efficiency of sequential cyclophosphamide-azathioprine in patients with SSc-ILD.

Currently, there are some promising agents such as mycophenolate mofetil (MMF) and rituximab that are being used with variable results. In small retrospective trials, MMF has also been found to result in improvement in skin score, stability in pulmonary functions and improved survival.[24-28]

Conclusions

Sequential treatment with intravenous pulse cyclophosphamide therapy for six months followed by azathioprine along with low-dose corticosteroids in patients with SSc-ILD showed significant improvement of pulmonary function and 6-minute walk distance at the end of 12 months follow-up. However HAQ-DI score improvement was not statistically significant. Due to the limitations of the study, firm recommendations regarding the optimum duration and dosage of drugs for the treatment of this condition cannot be made. In future, multi-centric, placebo-controlled, randomised studies are required for this purpose.

Acknowledgements

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