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Effect of glucocorticoid monotherapy on pulmonary function and survival in Japanese patients with scleroderma-related interstitial lung disease

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ABSTRACT

Background: Scleroderma-related interstitial lung disease (SSc-ILD) is a chronic, progressive condition that is characterized by a restrictive ventilator defect. Cyclophosphamide (CYC), with or without glucocorticoid, effectively alters the course of SSc-ILD. However, the effect of glucocorticoid monotherapy remains unclear.

Methods: Seventy-one patients with SSc-ILD were classified into 2 groups: 21 in the treatment group (glucocorticoid monotherapy [$n=14$] or immunosuppressive agents [$n=7$]) and 50 in the non-treatment group. Their backgrounds and prognoses were analyzed retrospectively. We also classified these patients into survival ($n=55$) and non-survival ($n=16$) groups to assess prognostic factors.

Results: The median follow-up period was 9.8 years. The treatment group had a greater proportion of patients with diffuse systemic sclerosis or respiratory symptoms than the non-treatment group. The treatment group's annual change in forced vital capacity (FVC) compared to baseline, which was 170.4 mL (157.8 mL for the glucocorticoid monotherapy subgroup and 191.3 mL for the immunosuppressive agent subgroup), was better than that of the non-treatment group, −60.8 mL ($p<0.01$). Still, in terms of 5- and 10-year survival, there was no statistically significant difference between these groups. No incidence of SSc renal crisis was reported in the treatment group. The non-survival group included more patients with pulmonary hypertension than the survival group, but multivariate analysis showed no other statistically significantly difference between these groups.

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Conclusions: Similar to CYC, glucocorticoid alone improved pulmonary function of Japanese SSc-ILD patients, suggesting that this monotherapy is a good alternative when CYC is contraindicated.

1. Introduction

Systemic sclerosis (scleroderma, SSc) is an autoimmune connective tissue disorder characterized by microvascular injury, excessive fibrosis of the skin, and distinctive visceral changes that can involve the lungs, heart, kidneys, and gastrointestinal tract [1]. Forty percent of these patients have a restrictive ventilator defect that results from interstitial lung disease (ILD) and is the most common cause of premature death from pulmonary hypertension (PH) [2–4]. The mortality rate among patients with severe ILD is especially high, approximately 42–70% within 10 years [1–4]. The most rapid decline in forced vital capacity (FVC) occurs within the initial 3 years after disease onset, indicating the presence of parenchymal lung injury and subsequent fibrosis [4].

At present, several agents have been evaluated as treatments for SSc-ILD. Daily oral ingestion or pulses of intravenous cyclophosphamide (CYC) were shown, in a large randomized, double-blinded, placebo-controlled trial, to suppress the decline of pulmonary function [5,6]. Glucocorticoid has also been widely used to treat SSc-ILD, and a combination of both medications, with intravenous CYC administration, has been effective [6,7]. However, given the lack of convincing benefit and the increased risk for SSc renal crisis, the use of glucocorticoid monotherapy is currently limited for individuals with SSc-ILD [8], and azathioprine is the alternative agent usually considered for patients with contraindications precluding the administration of CYC [9].

On the other hand, the majority of histopathological characteristics of SSc-ILD have been reported as a pattern of nonspecific interstitial pneumonia (NSIP), which includes varied degrees of alveolar wall inflammation and fibrosis with temporal homogeneity [10]. Patients' overall response to therapy directed toward ameliorating this pattern, and their related prognosis, are favorably related to those for idiopathic pulmonary fibrosis/usual interstitial pneumonitis (IPF/UIP) [10]. Accordingly, we usually manage idiopathic NSIP with immunosuppressive agents; that is, most of these patients' symptoms are controlled by glucocorticoid monotherapy [10,11]. Hence, for SSc-ILD, glucocorticoid alone could be effective. Because its efficacy and safety have never been documented, we conducted a retrospective cohort analysis at 2 major Japanese medical institutions to assess the effect of glucocorticoid monotherapy on pulmonary function and survival in patients with SSc-ILD.

2. Material and methods

2.1. Study sample

For this retrospective review, we surveyed all cases that were diagnosed as SSc-ILD in the Department of Respiratory Medicine at Juntendo University Hospital and Kameda Medical Center, a 1000-bed tertiary care center, from April 1996 to March 2009. We identified 71 patients with SSc-ILD, all of whom had undergone both a pulmonary function test and chest computed tomography (CT). We excluded patients who lacked imaging or pulmonary function data, or whose follow-up period was not verified as longer than 6 months. SSc was diagnosed by collagen disease specialists at each institution on the basis of clinical symptoms, physical histories and laboratory findings. Patients' co-morbidities were assessed with the Charlson Co-morbidity Index (CCI) [12]. The presence of ILD was confirmed by 2 pulmonologists and 1 radiologist, and we identified honeycomb lungs as "clustered cystic airspaces from several millimeters to 1 cm in size with well-defined, thick walls in the subpleural regions" [13]. We also assessed pulmonary arterial disease by transthoracic Doppler echocardiography and diagnosed PH when pulmonary artery systolic pressure was greater than 45 mm Hg [14].

Since CYC was reported as safe and effective [5], we have routinely treated SSc-ILD patients with the following initial regimen: 6 cycles of intravenous CYC (500 mg/m^2) monthly and oral prednisolone (PSL, 0.3–0.5 mg/kg). Before the efficacy and safety of CYC were reported [5], however, we administered an initial regimen of glucocorticoid monotherapy and PSL (0.5–1.0 mg/kg). However, we still used glucocorticoid monotherapy for patients with contraindications for CYC. In both regimens, the PSL dosage tapered down to 2.5–5 mg every 1–3 months, and the total duration of treatment was usually 1–2 years. Note that dosage and duration of therapy could be changed according to the patient's condition.

To assess the patients' clinical characteristics and prognoses, we grouped them according to whether they had received specific treatment for SSc-ILD. The 21 patients in the treatment group included 14 patients who had received glucocorticoid monotherapy and 7 who had received immunosuppressive agents, and the non-treatment group comprised 50 patients. Some patients in the non-treatment group were treated with very low doses of PSL (mean 2.7 mg daily) for cutaneous problems, but none received more than 10 mg of PSL per day. We then compared the groups with respect to background, disease course, and cause of death. All clinical information was obtained from medical records. Patients' data were used under the comprehensive consent from the patients of its use and the approval of IRB (2008/6/25).

2.2. Pulmonary function tests

Pulmonary function tests were performed according to American Thoracic Society standards, with an Autospirometer System 9 or Autospirometer System 21 (Minato Medical Science; Osaka, Japan) at Juntendo University Hospital or with Chestac-65V (Chest MI-Corp, Tokyo, Japan) at Kameda