Cyclosporin A in the Treatment of Acute Exacerbation of Idiopathic Pulmonary Fibrosis

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Abstract

Background Acute exacerbation (AE) of idiopathic pulmonary fibrosis (IPF) is considered to be a nearly fatal condition during the clinical course of IPF, as it is unresponsive to most conventional therapies.

Subjects and Methods To evaluate the efficacy of cyclosporin A (CsA) for AE of IPF, we conducted a retrospective study on autopsied IPF cases who developed AE and were treated with corticosteroids (CS) combined with CsA. The subjects comprised 11 males with a mean age of 69.9 years. The clinical features and prognosis of the CsA-treated group was compared to a group of 11 autopsied IPF cases with a mean age of 68.7 years who developed AE and were treated with CS alone (non-CsA-treated group).

Results Cs pulse therapy followed by CS maintenance treatment were conducted in all cases of AE. Patients in the CsA-treated group received in addition a low dosage of CsA (100-150 mg). Although 7 out of 11 patients in the CsA-treated group died of AE per se, 4 patients survived the AE. Only 2 patients died during the first episode of AE. In comparison, 7 out of 11 patients in the non-CsA-treated group died during the first episode of AE. The mean survival period after the first onset of AE was 285 days in the CsA-treated group and 60 days in the non-CsA-treated group. The prognosis of the CsA-treated group therefore was significantly better than that of non-CsA-treated group after AE of IPF.

Conclusion Administration of CsA combined with CS may be efficacious in the treatment of AE of IPF.

Key words: idiopathic pulmonary fibrosis, acute exacerbation, cyclosporin A, corticosteroids

Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive disease with a devastating prognosis and a median survival from the time of diagnosis of only 2-3 years (1). Although the disease is chronic in nature, one complication that has received little attention is an accelerated phase of the disease, namely acute exacerbation (AE) (2-6). It is a fulminant form of lung injury that leads to death in a period of a few weeks to a few months. AE of IPF has been defined as a condition with the following clinical characteristics: Under a previous or concurrent diagnosis of IPF, 1) exacerbation of dyspnea within 1 month, 2) newly developed diffuse bilateral ground-glass abnormality and/or consolidation superimposed on background reticular or honeycomb pattern consistent with the usual interstitial pneumonia pattern on high-resolution computed tomography, 3) deterioration of hypoxemia more than 10 torr from the previous level at rest, and 4) absence of apparent lung infection, pneumothorax, malignant tumor, pulmonary embolism or congestive heart failure (6). Recently, Collard et al (7) described the definition of AE in IPF as an acute, clinically significant deterioration in respiratory status of unidentified cause. This newly proposed diagnostic criteria requires endotracheal aspirate or bronchoalveolar lavage (BAL) to rule out respiratory infection or other identifiable etiologies as causes of the worsening condition (7).
AE is recognized to be a nearly fatal condition during the clinical course of IPF, as it is unreponsive to most of the conventional therapies such as corticosteroid (CS), and the patient eventually dies (2-6). The effectiveness of CS is thus limited, although CS has long been utilized for treating AE (2-7).

Previously, cyclosporin A (CsA) has been shown to be efficacious in the treatment of interstitial pneumonia (IP) associated with polymyositis and dermatomyositis (PM/DM) and other collagen vascular diseases that are refractory to CS therapy (8-13). Recent reports have also shown that CsA is efficacious in the treatment of AE of IPF (14, 15).

With this background, to evaluate the efficacy of CsA for AE of IPF, we conducted a retrospective study on 11 histologically-proven IPF cases who received CsA for the treatment of AE. As a control, 11 IPF patients with AE who had not been treated with CsA were also evaluated.

Subjects and Methods

Disease assessments and definitions

Of 233 consecutive patients with IPF who had been admitted from 1994 to 2004 at the Toranomon Hospital, 47 patients developed AE, and 22 out of 47 patients underwent postmortem examination. This study was a single-center retrospective study. These patients were enrolled by reviewing the medical records. The primary endpoint was defined as the survival time after AE.

Eleven cases of IPF were evaluated in the current study, they had developed AE and were treated with CS combined with CsA during the period from 1994 to 2004 (designated as the CsA-treated group). The clinical features and prognosis of the CsA-treated group were compared to those of 11 autopsied IPF cases who had developed AE but not received CsA treatment (designated as the non-CsA-treated group) during the same period. The demographic data of all patients in these two individual groups including clinical features, chest high-resolution CT (HRCT) scan images (i.e., CT score), pulmonary function tests, histopathological findings at autopsy, and prognosis were compared retrospectively.

The diagnosis of AE of IPF was made according to the criteria in previous reports as mentioned earlier (6). All patients underwent a postmortem examination to confirm the histopathological diagnosis of IPF. To rule out congestive heart failure and pulmonary embolism, the patients’ echocardiograms were recorded, and their serum levels of d-dimer and brain natriuretic peptide (BNP) were measured. Endotracheal aspiration or BAL had not been done in any of the patients due to severe respiratory failure. To investigate a potential infectious etiology, we evaluated whether bacteria or other opportunistic pathogens, such as *Pneumocystis Jirovecii* or cytomegalovirus, were present in induced spuata or venous blood.

Treatment

Methylprednisolone pulse therapy (1 g for 3 days) followed by CS maintenance treatment at a dosage of 0.5-1.0 mg/kg were administered to all patients. No later than 4 weeks after initiation of therapy, the CS dose was gradually reduced. In addition, patients in the CsA-treated group also received a low dosage of CsA (100-150 mg/day) starting at the same time as the pulse therapy. All patients in the CsA-treated group had signed an informed consent to receive CsA. Other patients received conventional CS monotherapy as mentioned above. Only one patient, in the non-CsA-treated group received mechanical ventilation, but other patients did not receive mechanical ventilation including non-invasive positive pressure ventilation. All patients received conventional oxygen therapy. Thus, there were no significant differences in ventilation therapy between the two groups.

The subjects in the CsA-treated group comprised 11 male individuals with a mean age of 69.9 years. The clinical features of the CsA-treated group were compared to those of the control group of 11 IPF patients who had developed AE but not received CsA treatment (non-CsA-treated group: 10 males and 1 female with a mean age of 68.7 years).

Clinical features

The evaluated clinical features included symptoms, smoking history, triggers of AE, laboratory findings, treatments, and prognosis. IPF was diagnosed based on the definition by the ATS/ERS international consensus statement regarding IIPs (1) and confirmed by postmortem examination. None of the patients had a history of other types of interstitial lung disease with known causes, such as exposure to toxic drugs, environmental dust, or complicated collagen vascular diseases. The diagnosis of AE of IPF was made according to the definition as mentioned before. The definitions of improved AE of IPF were as follows, 1) improvement of dyspnea, 2) improvement of hypoxemia by more than 10 torr at rest from the level at onset of AE, 3) as compared with the level at onset of AE, decreased diffuse bilateral ground-glass opacity and/or consolidation superimposed on background reticular or honeycomb pattern consistent with the usual interstitial pneumonia pattern on HRCT (improvement of CT ground-glass score to the same level ± 1) as before AE).

Concomitant medications

None of the patients received other immunosuppressive agents or interventions including azathioprine, cyclophosphamide, plasma exchange or sivelestat sodium hydrate. All patients received *Pneumocystis Jirovecii* pneumonia prophylaxis with trimetoprim–sulfamethoxazole (80 mg/400 mg daily), H2-blocker and osteoporosis prophylaxis. None of them received anticoagulant or antifibrotic therapy.

Pulmonary function tests

Lung volume and forced expiratory volume in one second (FEV1) were measured by the standard methods by using...
Chestac 55V (Chest Co. Ltd., Tokyo, Japan), and expressed as percent of the predicted value. These measurements were done prior to AE (within 1 year), but could not be repeated at or after AE because of the deteriorated conditions. The mean duration from the time of spirometry to the onset of AE was 6.6 months in the CsA-treated group and 6 months in the non-CsA-treated group. Arterial blood gas was analyzed with an ABL510 instrument (Radiometer Co. Ltd., Copenhagen, Denmark) before (within 6 months) and after AE in all cases. Arterial oxygen tension/inspiratory oxygen fraction (PaO2/FiO2) obtained from standard references were compared to those measured in the CsA-treated and non-CsA-treated groups before and after AE.

CT scan images

Chest HRCT scan images were evaluated before (within 6 months) and after AE by using the High Speed Advantage scanner (GE Medical Systems, Milwaukee, WI, USA). After AE, routine scanning of the entire lung was carried out with 10 mm thick sections. Additional thin-section CT with 1.0 mm section thickness was performed in all patients for analysis of parenchymal abnormalities. Thin-section CT images were reconstructed with a high spatial-frequency algorithm and were printed with the fixed window setting (lung center, -500 HU and width, 1,800 HU). The mean duration from the time of the CT scan to the onset of AE was 2.5 months in the CsA-treated group and 3.2 months in the non-CsA-treated group. The duration in these two groups showed no statistically significant difference. CT scans were reviewed independently by one thoracic radiologist and three pulmonologists who did not know the identity of the patients and other clinical, physiological, or pathologic parameters. The reviewing investigators initially scored the limited CT images by evaluating three images taken at the levels of the aortic arch, carina, and 1 cm above the diaphragm. Each lobe of the lung was scored at a scale of 0-5 for both alveolar and interstitial abnormalities according to the scheme described previously (16), depending on the extent of involvement in each lobe and the type of findings. Ground-glass opacity represented the alveolar findings (GGO score), and reticulation and honeycombing the interstitial findings (Fibrosis score). The scores for each lobe were averaged among all three investigators for data analysis.

Survival rates

The survival rate after the first onset of AE in the CsA-treated group was compared to that of the non-CsA-treated group by the log rank test and by plotting the Kaplan-Meier survival curves. All deceased patients underwent postmortem examinations.

Statistical analysis

All values were expressed as the mean ± standard deviation, and differences between subject groups were analyzed using the Mann-Whitney nonparametric U-test for two independent samples. All p values corresponded to two-sided tests and were considered statistically significant when less than 0.05. All analyses were performed with SPSS statistical software (version 13; SPSS, Inc., Chicago, IL).

Results

Patient backgrounds

The CsA-treated group comprised of 11 male individuals ranging from 61 to 81 years with a mean age of 69.9 years. The control non-CsA-treated group comprised of 10 males and one female ranging from 58 to 81 years with a mean age of 68.7 years. The duration from the onset of respiratory symptoms to AE was 36 ± 34 months in the CsA-treated group and 48 ± 46 months in the non-CsA-treated group. The durations of these two groups were not significantly different. All patients in these two groups manifested dyspnea, dry cough and hypoxia in less than 60 torr of room air. Inspiratory fine crackles were heard on physical examination in all cases at the time of AE. The smoking rate and the incidence of fever at the time of AE were slightly higher in the non-CsA-treated group (Table 1). The vital capacity (VC), %VC and partial oxygen pressure in arterial blood (PaO2) before AE in the CsA-treated group were 2.26 L ± 0.55 L, 72.4 ± 25.5% and 61.0 ± 21.0 torr, respectively, whereas those in the non-CsA-treated group were 2.19 ± 1.04 L, 72.0 ± 12% and 75.5 ± 14.5 torr, respectively. None of the parameters in these two groups were statistically different. None of the subjects were at risk for acute respiratory distress syndrome from exposure to toxic drugs, environmental dust, sepsis or acute renal failure, and none of them had any evidence of left ventricular dysfunction.

CT scoring before and after AE

The characteristic HRCT features of exacerbated IPF were diffuse bilateral ground glass opacity superimposed on UIP patterns (3-6, 17, 18). The mean fibrosis scores of each lobe before AE showed no statistical differences between the CsA-treated and the non-CsA-treated groups (upper: 1.63 ± 0.57 vs 1.63 ± 0.61, middle: 2.27 ± 0.69 vs 1.92 ± 0.45, lower: 4.02 ± 1.02 vs 3.93 ± 0.92) and the fibrosis scores were unchanged after AE in both groups (upper: 1.65 ± 0.64 vs 1.72 ± 0.67, middle: 2.22 ± 0.64 vs 1.81 ± 0.58, lower: 3.86 ± 1.17 vs 3.68 ± 1.19). In addition, the mean GGO scores of each lobe before AE also showed no statistically significant differences between the CsA-treated and the non-CsA-treated groups (upper: 1.88 ± 0.58 vs 1.22 ± 0.42, middle: 1.68 ± 0.73 vs 2.04 ± 0.56, lower: 2.72 ± 0.62 vs 2.93 ± 0.56). The GGO scores were significantly higher in both groups after AE (upper: 3.90 ± 0.67 vs 4.04 ± 0.72, middle: 4.72 ± 0.45 vs 4.72 ± 0.45, lower: 4.81 ± 0.39 vs 4.90 ± 0.29). Thus, the CT images of IPF before and after AE showed no apparent differences between the CsA-treated and the non-CsA-treated groups (Table 1).
Table 1. Patients Backgrounds at the Time of AE

<table>
<thead>
<tr>
<th></th>
<th>non-CsA-treated group</th>
<th>CsA-treated group</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>69.5 ± 11.5</td>
<td>71 ± 9</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>10:1</td>
<td>11:0</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>9/11 (31%)</td>
<td>6/11 (55%)</td>
</tr>
<tr>
<td>Dyspnea (%)</td>
<td>11/11 (100%)</td>
<td>11/11 (100%)</td>
</tr>
<tr>
<td>Dry cough (%)</td>
<td>11/11 (100%)</td>
<td>11/11 (100%)</td>
</tr>
<tr>
<td>Fever (%)</td>
<td>3/11 (27%)</td>
<td>3/11 (27%)</td>
</tr>
<tr>
<td>Fine crackles (%)</td>
<td>11/11 (100%)</td>
<td>11/11 (100%)</td>
</tr>
<tr>
<td>PaO2/FiO2 ratio</td>
<td>195±100</td>
<td>157±100</td>
</tr>
<tr>
<td>CT score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O2O2 score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>upper</td>
<td>4.04±0.72</td>
<td>3.90±0.67</td>
</tr>
<tr>
<td>middle</td>
<td>4.72±0.45</td>
<td>4.72±0.45</td>
</tr>
<tr>
<td>lower</td>
<td>4.90±0.29</td>
<td>4.81±0.39</td>
</tr>
<tr>
<td>Fibrosis score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>upper</td>
<td>1.72±0.67</td>
<td>1.65±0.64</td>
</tr>
<tr>
<td>middle</td>
<td>1.81±0.55</td>
<td>2.22±0.94</td>
</tr>
<tr>
<td>lower</td>
<td>3.68±1.19</td>
<td>3.06±1.17</td>
</tr>
</tbody>
</table>

Triggers of AE

Upper respiratory tract infection was the most common cause of AE in both groups (36% in the CsA-treated group and 55% in the non-CsA-treated group). Other causes were rapid dose reduction (>20 mg/month) of CS (9% in the non-CsA-treated group), surgical operation (AE developed at 6th postoperative days after surgical lobectomy for lung cancer) (9% in the CsA-treated group) and pleurodesis (18% in the CsA-treated group). No significant differences were noted between these two groups.

PaO2/FiO2

PaO2/FiO2 before (within 6 month) and after AE in the CsA-treated group were 290 ± 100 and 157 ± 100, respectively, and were 352 ± 62 and 195 ± 100 in the non-CsA-treated group, respectively. There were no significant differences in PaO2/FiO2 before and after AE between the CsA-treated and the non-CsA-treated groups (Table 1).

Treatment of IPF before AE

Before AE, 6 patients (54.5%) received no medication and only 3 (27.2%) were under CS maintenance treatment in the non-CsA-treated group. In contrast, 7 patients (63.6%) received no medication, and 2 (18.1%) were under CS maintenance treatment in the CsA-treated group before AE. There were no apparent differences in PaO2/FiO2 before and after AE between the CsA-treated and the non-CsA-treated groups (Table 1).

Pathological findings

The histopathological evaluation of lung specimens taken from patients who died of AE of IPF in both of the two groups presented a pattern of diffuse alveolar damage (DAD) such as the formation of hyaline membranes and alveolar type II cell hyperplasia. The UIP pattern was confirmed by the presence of patchy collagen fibrosis associated with scarring distributed in a peripheral and subpleural fashion, as well as honeycomb change. Evidence of superimposed DAD comprised areas of diffuse alveolar septal expansion and distortion by fibroblasts and myofibroblasts within the pale-staining matrix (acute phase of DAD). Proliferating spindle cells expanded and distorted alveolar septa with marked hyperplasia of pneumocytes, exudation of hyaline membranes, and squamous metaplasia of bronchiolar epithelium (organized phase of DAD) (4-7, 19-21, 23). Patients who died shortly after the onset of AE showed an acute phase of DAD, whereas those who survived the initial insult of AE but died of repeated AE afterward showed an organized phase of DAD (19-21, 23).

Prognosis

Although 7 out of 11 patients (63.6%) in the CsA-treated group eventually died of repeated episodes of AE, 4 (36.4%) survived after AE. Of the 4 surviving patients, three died of pneumonia and one died of chronic respiratory failure. Only 2 out of 11 patients died of the first episode of AE, and the other 9 responded to the initial treatments and survived. However, 5 cases experienced repeated AE and eventually died afterwards. In comparison, 6 out of 11 patients (63.4%) in the non-CsA-treated group died during the first AE, and the other 4 patients died during the following second AE. One out of 11 patients (9%) survived after AE but died of pneumonia afterward (Table 2). Only one patient in the non-CsA-treated group received mechanical ventilation. Other patients did not receive mechanical ventilation including non invasive positive pressure ventilation. None of the patients received other immunosuppressive agents or interventions including azathioprine, cyclophosphamide, plasma exchange, sivelestat sodium hydrate, or anticoagulant and antifibrotic therapy. Thus, there were no significant differences in the
Table 2. Prognosis after Acute Exacerbation

<table>
<thead>
<tr>
<th></th>
<th>non-CsA-treated group</th>
<th>CsA-treated group</th>
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<tbody>
<tr>
<td></td>
<td>number</td>
<td>mean survival after the onset of AE</td>
</tr>
<tr>
<td>Overall death by AE</td>
<td>10/11</td>
<td>61 (days)</td>
</tr>
<tr>
<td>Number of patients who died of AE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st</td>
<td>6/10</td>
<td>16 (days)</td>
</tr>
<tr>
<td>2nd</td>
<td>4/10</td>
<td>131 (days)</td>
</tr>
<tr>
<td>3rd</td>
<td>1/1</td>
<td>52 (days)</td>
</tr>
<tr>
<td>Survived after AE</td>
<td>1/11</td>
<td>60 (days)</td>
</tr>
</tbody>
</table>

AE: acute exacerbation
Five out of 22 patients survived after AE, but died of infection or chronic respiratory failure afterwards. All patients underwent postmortem examination.

Figure 1. Survival rate. The prognosis of the CsA-treated group was significantly better than that of the group without CsA treatment in acute exacerbation of IPF.

Interventional treatment such as mechanical ventilation or other adjunctive agents between these two groups.

The mean survival period after the first onset of AE was 285 days in the CsA-treated group and 60 days in the non-CsA-treated group. Thus, the prognosis of the CsA-treated group was significantly better than that of the group without CsA treatment after AE of IPF (Fig. 1). There were no significant differences between the two groups in survival after the diagnosis of IPF (mean survival time: 49.5 months in the CsA-treated group vs 44.8 months in the non-CsA-treated group), because the period from diagnosis of IPF to AE was slightly longer in the non-CsA treated group. On the other hand, the survival after the examination by spirometry in the CsA-treated group was significantly better than that in the non-CsA treated group (mean survival time: 463 days vs 241 days, respectively).

Discussion

IPF is a slowly but relentlessly progressing disease (1-7). The most common causes of death are respiratory failure and cor pulmonale generally resulting from advanced fibrotic lung disease (1-7). Patients with IPF may also suffer from acute respiratory deterioration related to complications with a known cause such as pneumonia, pneumothorax, and pulmonary embolism (1-7). However, a subset of IPF patients would experience an accelerated deterioration of the illness in the absence of any identifiable precipitating cause, namely, AE, which clinically resembles the acute respiratory distress syndrome (2-7, 19-24). In AE, laboratory findings suggest the presence of inflammation such as an increased number of neutrophils, elevated erythrocyte sedimentation rate, or C-reactive protein, but cultures of either sputum or autopsied lung specimens would turn out to be negative. Further, pathological samples investigated for infectious
agents by using monoclonal antibodies against cytomegalovirus, or special staining for *Pneumocystis Jirovecii*, fungi (Grocott’s methenamine silver stain), or acid-fast bacilli (Ziehl-Neelsen stain) are usually negative in AE (3, 5, 7).

The diagnosis of IPF in the present study was based on the clinical and/or radiographical criteria of ATS and was confirmed by the findings of UIP pattern on autopsy (1). For example, all cases had classical reticular and linear opacities with bibasilar and subpleural distribution in HRCT scans taken before AE. However, fibrosis and ground glass scores of CT scans were not significantly different between the CsA-treated and the non-CsA-treated groups before AE. After AE, all patients showed an increase in bilateral and diffuse ground glass opacities superimposed on UIP patterns (3-6, 17, 18). Eventually, ground glass scores were significantly increased in a similar fashion after AE in both the CsA-treated and the non-CsA-treated groups.

Importantly, superimposed DAD is the characteristic histopathology of AE of IPF (3-6, 19, 23). In this context, Rice and colleagues (19) concluded in a review of autopsy findings that AE associated with a histopathological pattern of DAD may be a common terminal event. In the current study, all autopsied lung specimens demonstrated the presence of DAD. The fact that all of our patients fell into respiratory failure with the emergence of new opacities on imaging studies and that only one patient received mechanical ventilation support the argument that DAD is the underlying pathological process of AE rather than a consequence of therapy such as ventilator-associated lung injury.

CsA primarily inhibits calcineurin by binding to calciphilin, a specific binding protein to calcineurin (25). Thus, calcineurin-dependent activation of the transcription factor, nuclear factor of activated T cells (NF-AT), is inhibited, and this suppresses expression of the most essential cytokine, interleukin 2 (IL-2), for T cell activation (25, 26). As T cells and alveolar macrophages play an important role in the pathogenesis of IPF, CsA may function as a modulator of the clinical course of IPF. CsA primarily inhibits calcineurin by binding to calciphilin, a specific binding protein to calcineurin (25). Thus, calcineurin-dependent activation of the transcription factor, nuclear factor of activated T cells (NF-AT), is inhibited, and this suppresses expression of the most essential cytokine, interleukin 2 (IL-2), for T cell activation (25, 26). As T cells and alveolar macrophages play an important role in the pathogenesis of IPF, CsA may function as a modulator of the clinical course of IPF. In contrast, suppression of IL-2 by CsA treatment requires interaction with the AP-1 (Fos/Jun) site (26). These facts suggest that the combination of CsA and CS suppresses the IL-2 gene expression in an independent, additive or perhaps synergistic fashion. Furthermore, CsA could inhibit proliferation of activated T cells on which Cs has little effect (26).

However, the effectiveness of CsA on IPF is controversial. Alton et al (27) reported a poor response to CsA after long-time use in patients with IPF, although the initial response was favorable. On the contrary, a study by Moolman et al (28) showed that 3 out of 5 patients responded to CsA and CS with an improvement in dyspnea and an increase in vital capacity 6 months after treatment. Regarding AE of IPF, Yoshimura et al (2) reported that all 35 patients who received a high dose of CsA died within one month after the onset of AE. Parambil et al (23) also reported that 6 out of 7 patients who received a high dose of CsA died of AE within a median duration of 29 days (20-57 days). The remaining one patient survived, but he eventually died of another episode of AE. Inase et al (14) also described their experience in treating 7 patients who received CsA in comparison with the outcomes of 6 IPF patients who did not receive CsA. Among those 7 patients treated with CsA, 4 survived for 14 to 64 months. In contrast, all 6 patients who did not receive CsA died within 15 months from the first onset of AE. We have also reported on the efficacy of CsA treatment in steroid-resistant and acutely exacerbated interstitial pneumonia (15). On the other hand, Okamoto et al reported that CsA therapy in combination with immunosuppressive agents did not significantly improve the prognosis in 15 patients who received CsA or cyclophosphamide in comparison with the outcomes of 9 patients who did not receive immunosuppressive agents in AE of IPF (29). In this context, the present study clearly demonstrated significant prolongation of the mean survival period after the first onset of AE of IPF/UIP in the CsA-treated group compared to that of the non-CsA-treated group. However, the present study was a retrospective analysis of an autopsied small number of patients, so it may underestimate the number of patients who had a good prognosis.

In conclusion, administration of CsA combined with Cs is a feasible and potentially efficacious treatment for AE of IPF. Further randomized controlled studies are necessary to determine the long-term effectiveness of the treatment.

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**References**


