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Long-term efficacy of macrolide treatment in idiopathic pulmonary fibrosis: a retrospective analysis

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Abstract. *Background and objective:* There is growing evidence for anti-inflammatory activities of macrolides in chronic respiratory diseases, such as diffuse panbronchiolitis, cystic fibrosis, or chronic bronchitis. The long-term effect of macrolides in idiopathic pulmonary fibrosis (IPF) is unknown. This study was aimed to investigate the effect of macrolide therapy on the frequency of acute exacerbation (AE) and the mortality in IPF. *Methods:* A total 52 IPF patients who were treated by combination of conventional agents with or without macrolides were retrospectively reviewed. The primary endpoint was the incidence of AE in IPF patients. We also observed survival rate after the treatment with or without macrolides. *Results:* AE was observed in 4 of 29 cases (13.8%) treated with macrolides and 8 of 23 cases (34.8%) treated without macrolides, respectively during 36 months. AE free survival rate of macrolide group was significantly better than that of non-macrolide group (logrank p=0.027). Survival rate of IPF patients with macrolide therapy was significantly better than that of patients without macrolide therapy (p=0.047). *Conclusion:* Our results indicate the potential beneficial efficacy of macrolide therapy combined with oral corticosteroids, immunosuppressive or anti-fibrotic agents in IPF. *(Sarcoidosis Vasc Diffuse Lung Dis 2016; 33: 242-246)*

Key words: idiopathic pulmonary fibrosis (IPF), acute exacerbation (AE), macrolides

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive interstitial pneumonia with a poor prognosis. The median survival of patients with IPF varies from 2 to 4 years after diagnosis and the major cause of death is respiratory failure due to IPF progression called "acute exacerbation (AE)" (1, 2). While there are no proven effective therapies for IPF to date, recent several clinical trials suggest that pharmacological treatment may prevent the progression or AE in IPF (3-9).

Macrolides have both antibacterial and anti-inflammatory activity (10-12). It has been suggested that the anti-inflammatory activity is not related to the antibacterial action because the anti-inflammatory effect is seen at low concentrations, below the minimal inhibitory concentration for airway bacteria (10). Macrolides are now used for long term in conditions such as cystic fibrosis to reduce airway inflammation (13, 14).

In the present study, we retrospectively evaluated whether long-term macrolide therapy reduce the frequency of AE in IPF patients. We also evaluated the survival rate of IPF patients after the conventional treatment with or without macrolides.

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Patients and Methods

Patients

We carried out a retrospective analysis of all IPF patients who were admitted to Nippon Medical School Hospital between January 2003 and December 2008. Excluded patients were those who could no be controlled during the follow-up period. The diagnosis of IPF was based on the criteria of the American thoracic Society/European Respiratory Society (ATS/ERS) international consensus statement (2): 1) exclusion of other unknown causes of interstitial lung diseases such as domestic and occupational environmental exposures, connective tissue disease, and drug toxicities; 2) the presence of a UIP pattern on high-resolution (HR) chest CT in patients not subjected to surgical lung biopsy; 3) specific combinations of HRCT and usual interstitial pneumonia (UIP) pattern in patients subjected to surgical lung biopsy. Acute exacerbation (AE) of IPF was defined as described previously (9, 15): exacerbation of dyspnea within one month, newly developing diffuse pulmonary opacities on chest radiographs, decrease in arterial oxygen tension (PaO_2) of more than 10 Torr under similar conditions, and absence of heart failure or an identified infectious agent. A total of 52 IPF patients were included in the study. Consecutive 29 IPF patients were treated by conventional agents with macrolides (erythromycin or clarithromycin). Comparable number of 23 IPF patients without macrolides pertaining to age, serum KL-6, pulmonary function tests, and conventional therapy during the same period were also included. We retrospectively analyzed the frequency of acute exacerbation and the survival of each group. Informed consent was obtained from all patients and the study protocol was approved by the local ethics committee at Nippon Medical School.

Statistical analysis

Data are summarized using mean ± SD. Patient demographics were compared between those patients receiving macrolides or not, using the two-sample unpaired t-test and Chi-square test. For survival analysis, time zero is defined as the index visit, which was the date the patient was first seen at Nippon Medical School Hospital during the study period. The survival rates after treatment with or without macrolides were compared by the log rank test and Kaplan-Meier survival curves were plotted. In all cases, statistically significance was defined as p values < 0.05. All statistical analyses were performed with Stat View 5.0 for Windows.

Results

Baseline characteristics of the 52 patients (10 female) with IPF are shown in Table 1. All patients were satisfied IPF diagnostic criteria of ATS/ERS (2). Twenty-nine IPF patients (7 female) were treated by conventional agents plus macrolides with a mean age of 67.2±6.3 years, and macrolide agents were as follows: clarithromycin (200-400 mg/day, n=27) and erythromycin (400 mg/day, n=2). Twenty-three IPF patients (3 female) were treated by conventional agents with a mean age of 69.1± 7.35 years. Diagnosis of UIP was made by surgical lung biopsy in three of 29 patients in macrolide and two of 23 patients in non-macrolide group, respectively. There are no differences between two groups except the value of serum LDH. Due to chronic respiratory failure, twenty of 29 patients (69.0%) with macrolide and thirteen of 23 patients (56.6%) without macrolide were receiving long-term oxygen therapy.

AE was observed in one case and two cases each in macrolide group and in non-macrolide group during 12 months, which was not significantly different. On the other hand, during 36 months AE was observed in 4 cases (13.8%) and 8 cases (34.8%) each in macrolide group and in non-macrolide group, respectively. AE free survival rate of macrolide group was significantly better than that of non-macrolide group (logrank p=0.027) (Fig. 1) during 36 months. Survival rate of IPF patients with macrolide therapy was significantly better than that of IPF patients without macrolide therapy (p=0.047) during 60 months (Fig. 2).

Discussion

This is the first retrospective study that suggested the beneficial effects of long-term macrolide therapy for reducing exacerbation frequency and mortality in patients with IPF.

Table 1. Characteristics of patients

	macrolide	non-macrolide	p value
Patients (n)	29	23	
Male/Female	22/7	20/3	
Age	67.2 ± 6.3	69.1 ± 7.35	† 0.32
Smoking status never/current or have smoked/ unknown	5/15/9	9/7/7	
Smoking Index	1020 ± 876 (n=15)	1229 ± 752 (n=7)	† 0.56
LDH (IU/L)	298.3 ± 98.6	245.0 ± 67.5	† 0.03
KL-6 (IU/ml)	1301.6 ± 738.5	1200.5 ± 806.2	† 0.64
Pulmonary Function Tests			
%VC	75.7 ± 15.2 (n=27)	75.7 ± 14.2 (n=23)	† 0.81
FEV1%	87.2 ± 7.01 (n=27)	85.9 ± 7.88 (n=22)	† 0.95
%DLco	55.2 ± 18.3 (n=24)	59.5 ± 23.2 (n=20)	† 0.4
Conventional therapy			
N-acetylcysteine inhalation	16	13	† † 0.92
Corticosteroids	12	7	† † 0.6
Immunosuppressants	4	4	† † 0.72
HOT (home oxygen therapy)	20	12	† † 0.22
pirfenidone	12	9	† † 0.23

† † Chi-square test
† unpaired t test

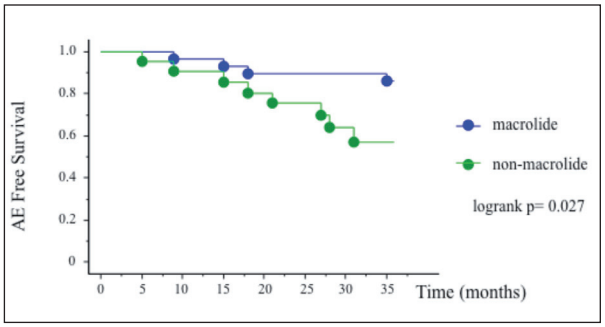

Fig. 1. Comparison of acute exacerbation free survival rates between the macrolide group (blue line, n=29) and the non-macrolide group (green line, n=23). (Kaplan-Meier method)

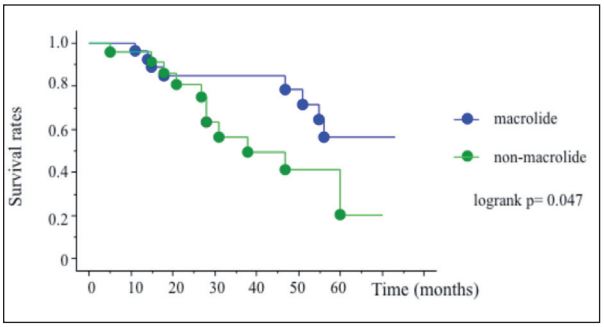

Fig. 2. Comparison of survival rates between the macrolide group (blue line, n=29) and the non-macrolide group (green line, n=23). (Kaplan-Meier method)

The incidence of AE in IPF patients has reported to be varied. In a series of 74 IPF patients, Kondoh et al. reported the one, two and three year incidence of AE was 8.6%, 12.6%, 23.9%, respectively (16). Of 461 IPF patients followed up for 22.9 months, the one and two year incidence of AE was 14.2% and 20.7% (17). In another study of 147 patients with biopsy-proven IPF, the one and two-year frequency of AE in was 8.5% and 9.6% (18). The differences of AE incidence in these studies may be explained by differences in AE criteria. In the present study with the revised AE criteria (9, 15), the one, two and three-year incidence of AE in IPF patients with macrolide therapy was 3.4%, 4.8% and 13.8%, respectively. This result suggested that long-term macrolide combined with conventional therapy could reduce the incidence of AE in IPF patients. This study also showed the significant improvement of overall survival in IPF patients with macrolide therapy followed up for 60 months.

To date he exact pathogenesis of AE in IPF patients remains unclear. Histological findings from lung specimens from IPF patients with AE show diffuse alveolar damage (DAD), which was also observed in patients with acute lung injury (ALI)/ acute respiratory distress syndrome (ARDS) (18, 19). Broncho- alveolar lavage in both IPF patients with AE and patients with ALI/ARDS revealed a predominant neutrophilia. The migration of activated neutrophils into alveolar sites is important in the process of AE in IPF or ALI/ARDS (18, 19). A recent report suggests that an association between macrolide use and improved survival in patients with ALI (20). Erythromycin has reported to inhibit neutrophil infiltration in lung injury model induced by bleomycin in rats (21). Li et al. also reported that 14-membered ring macrolides attenuated the migration of inflammatory cells such as neutrophils and lymphocytes in bleomycin-induced lung injury and fibrosis in mice (22). Moreover, macro ides accelerate apoptosis of Europhiles and the removal of cell debris by macrophages (23). Macrolide may have inhibitory effects on inflammatory cells especially neutrophils in IPF patients with AE or patients with ALI/ARDS. Several lines of evidence reported that macrolides had anti-inflammatory properties in other chronic respiratory diseases, such as diffuse panbronchiolitis, bronchial asthma, cystic fibrosis, or chronic bronchitis (24). Macrolides have reported to not only inhibit pro-inflammatory cytokines, such as tumor necrosis-alpha, IL-1 and nitric oxide but also increase the expression of IL-10, one of the most important anti-inflammatory cytokines (25). The effect of macrolides on inflammatory or anti-inflammatory cytokines is unknown in IPF patients with AE.

Long-term treatment with macrolides has been suggested to have several adverse events such as gastrointestinal symptom, ototoxicity, cardiac arrhythmias, and allergic reaction. In our study, no adverse event was observed as long as we could check in medical records during the study period.

Our study has certain limitations. First, the small number of Japanese patients represents a significant limitation in terms of reaching a general conclusion about the relationship between macrolide therapy and prevention of AE in IPF patients. Second, the retrospective study design means that IPF medication regimens and data collection were not systematically implemented. Conventional treatments for IPF were variable in the present therapy. IPF treatments combined with macrolides could affect the incidence of AE and survival. We need to evaluate the clinical efficacy of macrolides for IPF patients in a randomized control study.

In conclusion, the present study suggests the beneficial effect of long-term macrolide therapy on AE and survival in IPF patients. Further studies are needed to establish potential therapeutic benefits for macrolides in IPF.

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