Int J Clin Exp Med 2017;10(3):5805-5810
www.ijcem.com /ISSN:1940-5901/IJCEM0043187

Original Article

Chronic use of anti-reflux therapy improves survival of patients with pulmonary fibrosis

Bo Liu[1,2], Fang Su[3], Ning Xu[2], Tao Qu[2], Meixiang Li[2], Yuanrong Ju[4]

[1]Department of Respiratory, Shandong University, Jinan, China; Departments of [2]Respiratory, [3]Dermatology, Weihai Municipal Hospital, Weihai, China; [4]Shandong Provincial Hospital Affiliated to Shandong University, Jinan, China

Received August 1, 2016; Accepted November 22, 2016; Epub March 15, 2017; Published March 30, 2017

Abstract: *Objective:* Chronic micro-aspiration secondary to gastroesophageal reflux (GER) may play a role in the pathogenesis and natural history of idiopathic pulmonary fibrosis (IPF). Our goal was to investigate the relationship between chronic anti-reflux therapy and survival time in patients with IPF. *Methods:* Case reports comprising data involving gastroesophageal reflux diagnosis and treatment were analyzed to investigate the relationship between GER-related variables and survival time in an identified cohort of patients with IPF from Weihai Municipal Hospital. *Results:* Of the 69 eligible patients, 34 used varying doses of chronic anti-reflux medications, and 35 were non-users. Chronic anti-GER use was defined as ≥ 6 months non-prn use of any antacid drug and/or gastrointestinal motility drugs at study entry; non-users showed < 6 months of use or none. Chronic symptomatic use of anti-GER medications was significantly associated with longer survival time in unadjusted analysis (HR = 0.410, P = 0.003; HR = 0.524, P = 0.017). After adjustment, chronic use of GER medications was an independent predictor of longer survival time (HR = 0.229, P < 0.001). *Conclusions:* Chronic use of anti-reflux therapy is an independent predictor of longer survival time in patients with IPF.

Keywords: Idiopathic pulmonary fibrosis, anti-reflux therapy, micro-aspiration, gastroesophageal reflux

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive fibrosing interstitial pneumonia of unknown etiology occurring in adults. Radiological and histopathological manifestations are consistent with interstitial pneumonia [1]. The quality of life in patients with IPF is dismal, with a median survival time of only 3 to 5 years following diagnosis [2].

Emerging data support a role for chronic micro-aspiration in the pathogenesis and natural history of idiopathic pulmonary fibrosis. Two small case series have suggested stabilization of pulmonary function with medical or surgical treatment of GER [3, 4]. In 2011, a retrospective study showed that antacid treatment prolonged the survival time in patients with IPF [5].

However, acid suppression therapies increase non-acid reflux and do not effectively prevent from acid reflux [6]. The aim of this study was to investigate the role of combination therapy comprising antacids and gastrointestinal motility drugs in the survival of patients with IPF

Patients and methods

Study design and patient population

Among 145 cases of diffuse interstitial lung disease (ILD), 69 with IPF were selected as the research subjects, in accordance with the 2002 American Thoracic Society (ATS)/European Respiratory Society (ERS) non-traumatic diagnostic standard[1]. The patients were identified from inpatients and outpatients of Weihai Municipal Hospital since January 2001 to January 2008. IPF diagnosis required the absence of an identifiable etiology for ILD and radiologic evidence of interstitial pneumonia. Serological markers were excluded from other diffuse interstitial lung diseases based on diagnosis by two respiratory disease experts. All IPF patients in the cohort, who had pulmonary function tests every 3 months, were eligible for

Table 1. Baseline demographics (N = 69)

Variable	Value
Age, y	68 (SD, 6)
Male sex	46 (67%)
BMI, kg/sq.m	27 (SD, 2)
Ever smoker	50 (73%)
FVC, % predicted	71 (SD, 15)
DLCO, % predicted	52 (SD, 15)
Gastroesophageal reflux symptoms[1]	24 (35%)
Gastroesophageal reflux disease[2]	47 (68%)
Gastroesophageal reflux medication use[3]	35 (49%)

[1]Patient reported symptoms of heartburn or regurgitation. [2]Patient or physician reported this diagnosis. [3]Proton pump inhibitor (n = 32); H2 blocker (n = 2); no patient was taking both; combination of anti-acid drugs and gastrointestinal motility drugs (n = 16); anti-acid therapy alone (n = 18).

inclusion. Eligible patients were excluded only if survival data were unobtainable (missing in three subjects). The patient's demographic data, history of tobacco use (classified as never or ever), body mass index (BMI), lung function, and anti-reflux drugs (inhibitory to acid reflux drugs and gastrointestinal motility drugs) were recorded in the form of a case report. JAEGER® MasterScreen™ PFT system (Würzburg, Germany) was used for pulmonary function testing, including FEV, FVC, DLCO and lung volume.

Among the 69 patients, 34 received chronic anti-reflux therapy: 16 patients were treated with a combination of antacid and gastrointestinal motility drugs, and 18 patients were treated with antacid therapy alone. Chronic anti-reflux therapy was defined as ≥ 6 months non-prn use of any antacid and/or gastrointestinal motility drugs, such as H2 blocker, or proton pump inhibitor (PPIs) or mosapride or domperidone. PPIs were administered to 32 patients and histamine-2 blockers (H2B) were given to the other two patients. Non-users underwent less than 6 months of treatment or none. GER symptoms, GER disease, and GER medication use were recorded and reviewed prospectively by the treating physicians during the hospital visit. Prospective and systematic data of medication use were acquired via standardized questionnaires and physician review. All the patients were followed up until the end of February 2015 for clinical symptoms, lung function, high-resolution CT examination of chest, and the use of anti-reflux drugs. Patients unable to visit the hospital were followed up by telephone. If the patient died, the time of death was recorded and the cause of death determined. Enrollment into the cohort was based on informed consent to record clinical data and review medical records. Demographics, clinical features, medication history, pulmonary function, were obtained for all patients. The Weihai Municipal Hospital ethics committee approved the protocol.

Statistical analysis

SPSS 19 statistical software was used for data processing and analysis. Descriptive statistics are presented as mean and standard deviation (SD) or median (25^{th} percentile, 75^{th} percentile). Comparisons between groups were performed using the t test, Mann-Whitney rank sum test, chi-square test, or Fisher's exact test as appropriate. Survival time was calculated from the initial visit (time of diagnosis) until the primary outcome was achieved, either death or loss to follow-up. Cases surviving until the last follow-up day, missing and dead cases involving non-IPF disease were managed by censoring statistical data. Survival time (in days) was reported as median (25^{th} percentile, 75^{th} percentile). Unadjusted and adjusted Cox proportional hazards regression analyses were performed. The survival curves were plotted by Kaplan-Meier method, and the differences were tested using the log rank test. The adjusted Cox regression modeling was performed using all the significant predictors in unadjusted analysis and also using stepwise selection. All tests were two-sided and were performed at a significance level of 0.05.

Results

Study population

The study cohort consisted of 69 patients (male 46/female 23). The mean age was 68 y. The mean body mass index (BMI) was 27. Fifty patients were current or former smokers (73%). Mean baseline forced vital capacity (FVC) was 71% predicted and diffusing capacity of the lung for carbon monoxide (DLCO) was 52% predicted. Symptoms of GER were present in 24 (35%) patients. Patient reported history of GER disease was present in 47 (68%) patients. At the time of diagnosis, 35 (49%) patients reported current treatment with anti-reflux therapy

Table 2. Unadjusted predictors of survival (Univariate Cox proportional hazard analysis results)

Variable	HR (95% CI)	*P* Value
Age	1.116 (1.057-1.178)	< 0.001
Male sex	0.91 0 (0.520-1.591)	0.740
BMI	0.758 (0.657-0.875)	< 0.001
Ever smoker	1.317 (0.736-2.357)	0.353
Long-term oxygen	4.509 (2.398-8.480)	< 0.001
FVC, % predicted	0.890 (0.865-0.916)	< 0.001
DLCO, % predicted	0.878 (0.848-0.908)	< 0.001
Gastroesophageal reflux symptoms[1]	0.410 (0.229-0.736)	0.003
Gastroesophageal reflux disease[2]	1.485 (0.844-2.613)	0.170
Gastroesophageal reflux medicationuse[3]	0.524 (0.308-0.890)	0.017

Abbreviations: BMI, body mass index; DLCO, diffusing capacityfor carbon monoxide; FVC, forced vital capacity. [1]Patient reported symptoms of heartburn or regurgitation. [2]Patient or physician reported this diagnosis. [3]Proton pump inhibitor (n = 32); H2 blocker (n = 2); no patient was taking both; combination of anti-acid drugs and gastrointestinal motility drugs (n = 16); anti-acid therapy alone (n = 18).

Table 3. Adjusted predictors of survival (Multivariate Cox regression analysis)

Variable	HR (95% CI)	*P* Value
FVC, % predicted	0.952 (0.907-0.999)	0.047
DLCO, % predicted	0.887 (0.836-0.940)	< 0.001
Gastroesophageal reflux medication use[1]	0.229 (0.118-0.442)	< 0.001

Abbreviations: DLCO, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity. [1]Proton pump inhibitor (n = 32); H2 blocker (n = 2); no patients were taking both; combination of antacids and gastrointestinal motility drugs (n = 16); antacid therapy alone (n = 18).

Table 4. Comparison of IPF patients treated with and without gastrointestinal medications

Variable	Taking GER Medications (n = 34)	Not Taking GER Medications (n = 35)	*P* value
Age, y	67 (SD, 7)	70 (SD, 5)	0.072
Female sex	12 (35.3%)	11 (31.4%)	0.496
BMI, kg/m^2	26.5 (SD, 1.7)	26.8 (SD, 2.1)	0.788
Ever smoker	23 (67.6%)	27 (77.1%)	0.377
Long-term oxygen	10 (28.6%)	11 (32.4%)	0.733
FVC, % predicted	74.2 (SD, 12.9)	68.8 (SD, 16.3)	0.139
D LCO, % predicted	54.2 (SD, 13.2)	49.7 (SD, 15.7)	0.133
Gastroesophageal reflux Symptoms[1]	13 (38.2%)	11 (31.4%)	0.553
Gastroesophageal reflux Disease[2]	26 (76.5%)	21 (60.0%)	0.142

Abbreviations: BMI, body mass index; DLCO, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity. Data are expressed as mean (SD), n (%), or median (25th percentile, 75th Percentile). [1]Patient reported symptoms of heartburn or regurgitation; [2]Patient or physician reporting this diagnosis.

(antacids and/or gastrointestinal motility drugs) (**Table 1**). Sixty-five (94%) patients used PPI as routine antacid therapy.

Survival analysis

Results of univariate Cox proportional regression analysis of unadjusted predictors of survival time are listed in **Table 2**. The reported presence of GER symptoms, GER medication use, BMI of the patients, DLCO% predicted, FVC% predicted, with a hazard ratio less than one, were associated with longer survival. The hazard ratio of age and long-term oxygen use, were all higher than 1, which suggested negative correlation with patient prognosis. The reported presence of GER disease, gender, and smoking, was not significantly correlated with survival.

The results of the adjusted multivariate Cox regression analysis using a stepwise regression model showed that higher DLCO% predicted, higher FVC% predicted, and the use of anti-reflux medications were associated with longer survival (**Table 3**). Other variables such as age, BMI, the reported presence of GER symptoms and long-term oxygen consumption, were not evaluated.

Comparison of anti-reflux therapy usage

There were no significant differences in age, BMI, history of smoking, gender, long-term oxygen use, or pulmonary physiology between patients with and without reported anti-reflux therapy (**Table 4**). Anti-reflux therapy was associated with a median survival time of 929 days com-

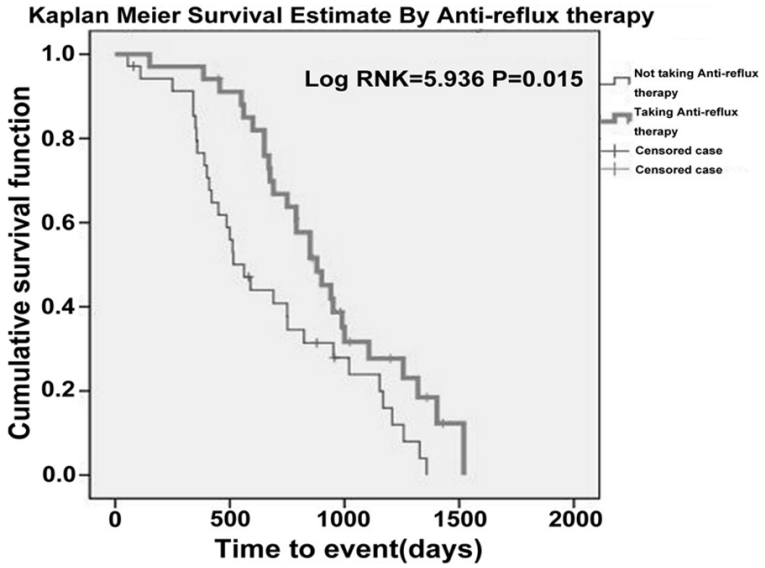

Figure 1. Patients undergoing anti-reflux therapy survived significantly longer than the patients without anti-reflux therapy.

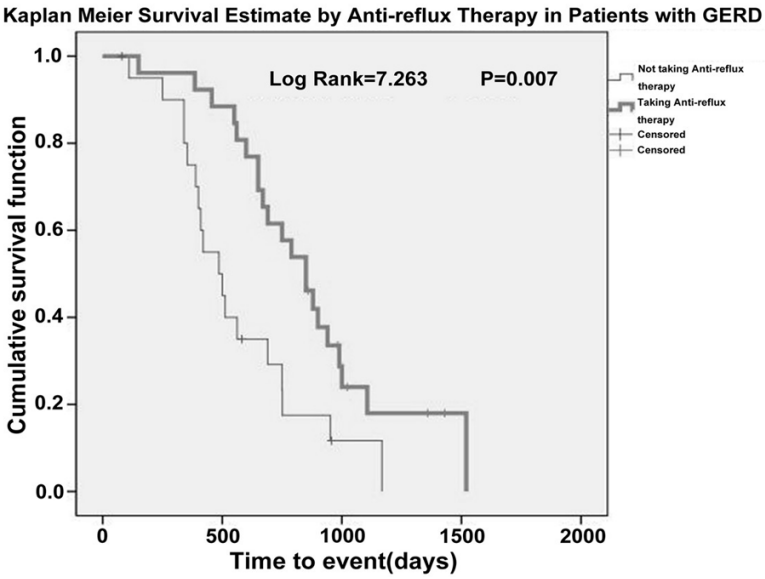

Figure 2. Patients with GERD undergoing anti-reflux therapy survived significantly longer than the patients without anti-reflux therapy.

pared with a median survival time of 685 days in patients without such therapy. Patients undergoing anti-reflux therapy survived significantly longer than the patients without anti-reflux therapy (Log Rank = 5.936, P = 0.015) (**Figure 1**). After further stratification analysis, it was found that in patients with or without GERD, anti-reflux treatment resulted in longer survival than in patients without anti-reflux treatment. The difference was far more significant in patients with GERD (Log Rank = 7.263, P = 0.007) (**Figure 2**). In patients with a reported presence of GER symptoms, there was no significant difference in survival time following anti-reflux therapy compared with patients without anti-reflux therapy (Log Rank = 0.592, P = 0.441). However, in patients reporting absence of GER symptoms, survival with anti-reflux therapy was not significantly longer than in untreated patients (Log Rank = 1.617, P = 0.204) (**Figure 3**). In patients undergoing anti-reflux therapy with the combination of anti-acid and gastrointestinal motility drugs, the survival was significantly longer than in those treated with antacids alone (Log Rank = 12.103, P = 0.001) (**Figure 4**).

Discussion

In this study, we found that the survival of IPF patients with anti-reflux treatment was longer than in those without anti-reflux treatment. Our study supported the hypothesis that GER and chronic micro-aspiration played an important role in the pathophysiology of IPF. Suppressing gastric acidity may reduce the injury caused by micro-aspiration. Our results are consistent with several previous studies. A retrospective case series described four patients with IPF, clinically stabilized over several years with medical and/or surgical therapy targeted at adequate suppression of gastroesophageal reflux [4]. More recently, another case series of 14 patients with progressive IPF who underwent laparoscopic Nissen fundoplication showed stabilization of oxygen requirements, without any changes in pulmonary function [7]. Two larger cohort studies found that treatment of GER may slow disease progression and improve survival of IPF

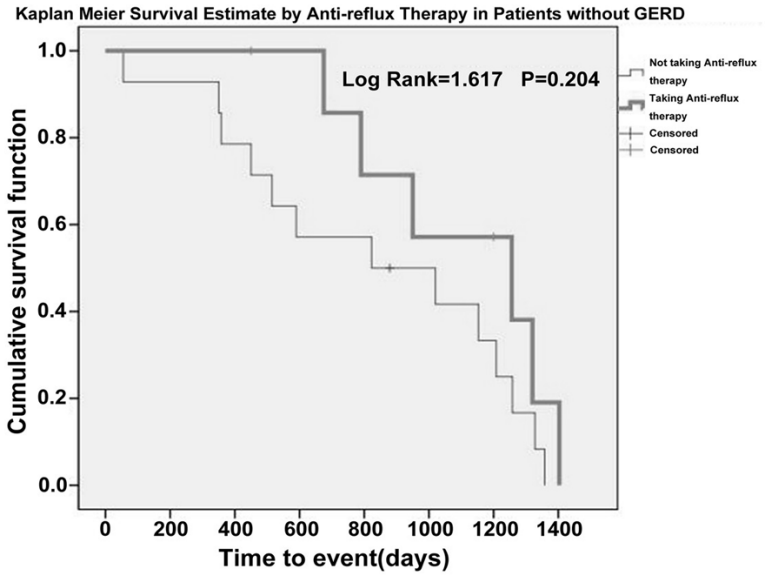

Figure 3. Patients without GERD undergoing anti-reflux therapy did not survive longer than the patients without anti-reflux therapy.

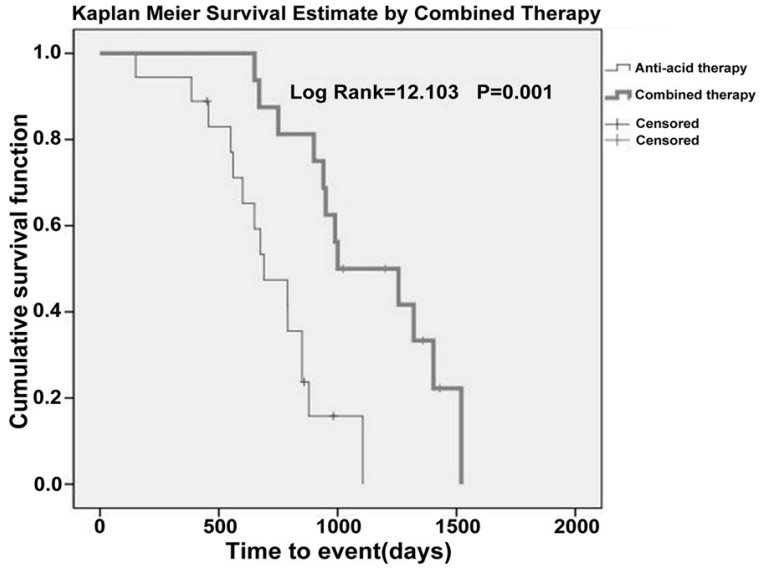

Figure 4. In patients undergoing anti-reflux therapy with the combination of anti-acid and gastrointestinal motility drugs, the survival was significantly longer than in those treated with antacids alone.

patients [5, 8]. The use of medical therapy for GER slowed the decline in FVC with fewer acute exacerbations copared with those who without receiving medical therapy for GER. The use of medical therapy for GER (e.g., PPIs or H2B) was an independent predictor of longer survival which was found in another study of 204 patients with IPF enrolled prospectively in longitudinal cohort studies.

A study by Ho and colleagues extended the beneficial effect of PPIs beyond neutralization of highly acidic gastric juice. They showed that PPI inhibition of dimethylarginine dimethylaminohydrolase and inducible nitric oxide synthase [9-11]. In our cohort study, most of the patients underwent PPI inhibition using anti-reflux drugs, which may explain the survival benefits of patients treated with antacids.

Our results may be affected by several intangible factors, such as pulmonary rehabilitation, influenza vaccination, or more comprehensive care. The indication for GER medication use in this cohort was unknown. Our cohort had limited data pertaining to GER diagnosis and responsiveness to treatment. Data related to 24-h pH and/or esophageal impedance testing, dosing, and compliance with GER therapy, and the side-effects of acid suppression should be collected in future studies.

Until now, no concrete pathogenic link between gastroesophageal reflux and IPF has been identified, and antacid treatment has inconsistent effects on survival [12]. A randomized placebo-controlled trial of patients with IPF, agent-specific and dose-dependent therapeutic outcomes is needed to better define individuals who benefit from such interventions.

In conclusion, our findings suggest that chronic use of anti-reflux therapy is an independent predictor of longer survival time in patients with IPF, especially including prokinetic therapies, rather than acid suppression therapy alone.

Disclosure of conflict of interest

None.

Address correspondence to: Yuanrong Ju, Shandong Provincial Hospital Affiliated to Shandong University, No. 324 Jinwuweiqi Road, Jinan 250021, Shandong, China. Tel: +86-13964066157; E-mail: juyrsd@163.com

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