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The effect of anticoagulant therapy for idiopathic pulmonary fibrosis in real life practice

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Abstract. *Background:* IPF is a common form of interstitial lung disease for which there is no effective therapy and usually results in death. Two previous contradictory studies showed anticoagulant therapy to be associated with both improved and worsened survival, respectively. *Objective:* The objective of this retrospective cohort study was to evaluate the effect of anticoagulant therapy on the survival and disease progression of patients with idiopathic pulmonary fibrosis (IPF) in real clinical practice. *Methods:* We compared the clinical characteristics, time to disease progression, incidence of acute exacerbation, and survival of 25 (20%) IPF patients receiving anticoagulant therapy to the remaining 97 IPF patients not receiving anticoagulant therapy. In addition we conducted a sensitivity analysis using as comparator a group of 25 patients matched by age, sex, functional impairment, cardiac comorbidities and pulmonary hypertension. *Results:* Patients on anticoagulant therapy had a worse 1- and 3-year survival (84% and 53% versus 89% and 64% in the non-anticoagulant group, respectively), a difference that persisted after adjusting for age and comorbidities (hazard ratio 3.1 - 95% confidence interval, 1.4 to 7.0; p=0.006) and after comparison with the matched group (adjusted HR=4.8, 95% CI: 1.8-12.8; p=0.002). IPF patients on anticoagulant therapy had a shorter interval to disease progression (0.7 years versus 1.6 years, adjusted HR 2.2 -95% CI, 0.96 to 5.1; p=0.063) confirmed also in the analysis with matched subgroups (HR=2.7 (95% CI: 1.2-6.5); p=0.023). The incidence of acute exacerbations did not differ in the two groups (22% versus 23%). Two patients (8%) experienced anticoagulant treatment related complications and included an episode of hemorrhagic shock. *Conclusion:* In this retrospective study patients treated with anticoagulants had a worse survival and a shorter interval to disease progression. This support the recent finding that warfarin worsen the respiratory status and survival of IPF patients. *(Sarcoidosis Vasc Diffuse Lung Dis 2013; 30: 121-127)*

Key words: anticoagulant therapy, idiopathic pulmonary fibrosis, real life practice

Introduction

Idiopathic pulmonary fibrosis (IPF) is a form of idiopathic interstitial pneumonia characterized by the presence of histopathologic or radiologic pattern of usual interstitial pneumonia (UIP). It is a relentlessly progressive lung disease usually resulting in death, with a median survival of 3 years (1, 2). No antiinflammatory or antifibrotic agent tested in rigorously controlled prospective trials has shown improved survival for patients with IPF (1).

Recent studies suggest that IPF results from sequential lung injury and subsequent aberrant wound healing without significant inflammation (3-5). The observation that activation of coagulation proteases and fibrin deposition play an important role in lung injury and the recent finding that venous throm-

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boembolism is associated with idiopathic interstitial pneumonias generated interest on the therapeutic role of anticoagulant therapy in patients with IPF (6, 7).

Anticoagulants are used in the management of cardiovascular diseases and have proven benefit in primary and secondary prevention of venous thromboembolism. In experimental models of lung fibrosis, treatment with thrombin inhibitors, activated protein C and aerosolized heparin have shown potential benefits (8,9). However prospective clinical trials on anticoagulation report contradictory results. A single prospective nonblinded study showed that anticoagulant therapy was associated with improved survival in patients with IPF (10). The nonblinded design of this study and the selection bias of a cohort that was not representative of the general IPF population have generated concerns as to the validity of the study results and anticoagulant therapy has not been broadly adopted as a treatment for IPF (1, 11). The NIH has funded a prospective randomized double blind placebo controlled trial of warfarin therapy for IPF (ACE-IPF) that was aborted before the study endpoint due to a low probability of benefit and to an increase in mortality in the warfarin-treated subjects (12, 13). The results of this trial are of great interest. However clinical trial may significantly diverge from real life settings and results may not always give all appropriate answers. This is particularly true for this trial where warfarin was used with the intention to treat IPF, whereas in clinical practice warfarin is often used in IPF patients for other indications. Therefore based on current evidence it remain to be addressed what is the impact of warfarin treatment in a hospital-setting based cohort of patients in whom warfarin is used for acknowledged indications. Our retrospective study is an attempt to see whether anticoagulant therapy as used in current clinical practice is associated with any signs of benefit for IPF patients. We compared the clinical characteristics, time to disease progression, incidence of acute exacerbation, and survival of IPF patients receiving anticoagulant therapy to those not receiving anticoagulant therapy.

Materials and Methods

This study was approved by the Area Vasta Romagna Review Board. Systematic search of the patient database of Pneumology Unit at GB Morgagni Hospital, Forlì, Italy, revealed 203 patients who satisfied the current diagnostic criteria for IPF and followed by our IPF unit during the period of January 1, 2000, to December 31, 2009. IPF was defined by criteria for "definite IPF" as outlined in current guidelines (1). Acute exacerbation was defined as acute respiratory worsening for which a cause could not be identified and meeting all criteria for as proposed by Collard et al (14). Disease progression was defined as a 10% decline in FVC or 15% decline in DLco documented by at least two consecutive pulmonary function tests. We designated as progression of disease only cases in which known causes of pulmonary worsening could be excluded (pneumonia, infections, cardiovascular events, thoracic surgery, others). Patients with known causes of pulmonary fibrosis were excluded from this analysis, including those with connective tissue diseases, relevant environmental or inhalational exposures, radiation therapy to the thorax, and exposure to fibrogenic drugs. All outside medical record were collected and reviewed by pulmonologists of our institution.

The following data were collected from the medical records: date of the first visit at our institution during which the diagnosis of IPF was established, age, gender, medications, smoking history, physical examination findings, laboratory results, pulmonary function data, high-resolution CT results, bronchoscopy and lung biopsy and the presence of the following comorbidities: atrial fibrillation coronary artery disease, congestive heart failure, myocardial infarction, pulmonary arterial hypertension, pneumonia, lung cancer, number of hospitalization at our institution for IPF-related complications. Pulmonary arterial hypertension was evaluated by echocardiography and defined as estimated systolic pulmonary artery pressure ≥ 36mmHg. Anticoagulant treatment and treatments for IPF prior to and after the index visit date at our institution, including oxygen therapy, were also documented. Patients were contacted in July 2010 to assess vital status and complete follow-up by phone calls, public record review, Italian death registry review and review of subsequent patient visits.

Statistical Methods

Patient demographics and characteristics were compared using the two-sample rank sum test for

continuous variables and the chi-square (exact) test for categorical variables. Cumulative time to event distributions (survival, progression, acute exacerbation) were estimated using the Kaplan-Meier method. Time to event outcomes was compared between the anticoagulation and non-anticoagulation groups using time dependent proportional hazards regression models. In all cases p-values <0.05 were considered statistically significant.

Results

Patient Characteristics

IPF was diagnosed in 203 patients of which 81 patients, lacking clinical data as above mentioned and/or a detailed drug history, were excluded from analysis. Characteristics of the remaining 122 patients are reported in Table 1. Among these 122 patients twenty five (20%) were treated with anticoagulant therapy (warfarin therapy to maintain the prothrombin international normalized ratio between 2 and 3). Seventeen patients were receiving anticoagulant treatment for pulmonary hypertension secondary to IPF, four patients for pulmonary embolism, one patient for coronary artery disease, and three patients for atrial fibrillation. Median duration of anticoagulation therapy was 316 days (range, 36-1921 days).

In table 1 are summarized the characteristics of the three comparator groups: anticoagulant-treated population (N=25), matched untreated group (N=25) and non-matched untreated group (N=72). There was no difference in gender, cigarette smoking history, pulmonary function assessment and oxygen use at rest. Patients in the anticoagulant group were slightly older compared to the non-matched untreated group. Patients in the anticoagulant group were more prone to be hospitalized and carried a heavier burden of comorbidities, particularly cardiovascular diseases (heart failure), pulmonary embolism and pulmonary arterial hypertension compared to the non-matched untreated group. Twenty three patients among the twenty-five patients of the anticoagulant group (92%) had pulmonary arterial hypertension, median pulmonary systolic pressure (sPAP) was 45mmHg (range 21-100). Whereas only 48% of non-matched untreated patients had pulmonary hypertension (median sPAP 33, range 15-71). Comparing the treated group with the matched subgroup of 25 untreated patients there were no differences in age, gender, smoking status, FVC% of pred,, DLco % of pred., GAP index, Oxygen use at rest, comorbidities and pulmonary arterial hypertension. The three groups of patients received treatment for IPF (Table 2) according to the ATS/ERS guidelines and to our standard clinical practice at that time. Patients in the anticoagulant group were more frequently treated with azathioprine and less frequently treated with prednisone.

Survival to Death

Among the 25 patients in the anticoagulant group, 12 died (median 3.5 years). All twelve patients died of IPF (3 died of acute exacerbation, 9 died of progression of IPF to terminal respiratory failure). Of the 97 patients in the non-anticoagulant group, 30 died (median survival 4.9 years). One and three year survival among the two groups were 84% and 53% in the anticoagulant group and 89% and 64% in the non-anticoagulant group, respectively. There was a significant difference in survival between the two groups (unadjusted hazard ratio [HR] = 3.4 [95% confidence interval [CI], 1.7 to 6.7; p <0.001] (Fig. 1). After adjusting for age and any cardiovascular comorbidities the hazard ratio was 3.1 (95% CI, 1.4 to 7.0; p=0.006). This difference is even more striking when comparing the two matched groups of 25 patients treated and not treated with warfarin (HR=5.9 (95% CI: 2.3 – 15.1); p<0.001, Adjusted: HR=4.8 (95% CI: 1.8-12.8); p=0.002).

Progression free survival

Median follow-up duration was 1008 days (range, 211-3538) in the anticoagulant group and 759 days (range, 31-2945) in the non-anticoagulant group. During the follow-up period 17 patients among 19 patients on anticoagulant therapy with data available (89%) and 50 among 71 non-anticoagulant subjects with data available (70%) experienced disease progression, as previously defined. Median time to disease progression was 0.7 years in the anticoagulant group and 1.6 years in the non-anticoagulant group. There was a significant difference

Table 1. Baseline characteristics of the patients and hospitalizations during follow-up

	Anti-coagulation N=25	NO Anti-coagulation N=97		p-value
		Matched group N=25	Not matched group N=72	
Age	66.9 (50.7-80.11)	65.9 (53.5-81.3)	61.7 (38.5-83.7)	0.047
Male	17 (68%)	17 (68%)	53 (74%)	0.68
Smoking status		0.59		
Never	10 (40%)	10 (40%)	18 (25%)	
Former	15 (60%)	15 (60%)	51 (71%)	
Current	0	0	2 (2.8)	
Pack Years	7 (0-60)	14 (0-90)	18 (0-90)	0.096
UIP diagnosis		0.44		
SLB	8 (32%)	12 (48%)	41 (57%)	
HRCT	17 (68%)	13 (52%)	31 (43%)	
PFTs:				
FVC	79 (45-109)	75 (51-116)	77 (22-146)	0.79
FEV1	81 (55-131)	81 (54-126)	80 (29-151)	0.9
DLco	46 (24-75)	47 (23-125)	51 (27-89)	0.06
TLC	63 (41-96)	63 (49-101)	69 (39-102)	0.6
GAP index		0.054		
I	11 (44%)	12 (48%)	46 (67%)	
II	9 (36%)	12 (48%)	18 (26%)	
III	5 (20%)	1 (4%)	4 (6%)	
Oxygen use at rest	2 (8%)	2 (8%)	4 (6%)	0.68
Comorbidities				
CHF	10 (40%)	7 (28%)	0	<0.001
MI	4 (16%)	3 (12%)	8 (12%)	0.74
CAD	7 (28%)	5 (20%)	12 (18%)	0.31
PE	4 (16%)	0	0	0.002
PH	23 (92%)	25 (100%)	26 (48%)	<0.001
Hospitalizations		<0.001		
0	6 (24%)	4 (16.7%)	20 (30%)	
1	4 (16%)	10 (42%)	26 (39%)	
2	15 (60%)	10 (42%)	19 (29%)	
3	0	0	1 (2%)	

Values are N (%) or median (range). P-value is from chi-sqaure (exact) test or two-sample rank sum test as appropriate and is calculated between the two comparator group: 25 treated patients and 97 untreated patients. Abbreviations: UIP usual interstitial pnemumonia, HRCT high resolution computed tomography, SLB surgical lung biopsy, FVC forced vital capacity, FEV1 forced expiratory volume, DLco diffusion of carbon monoxide, TLC total lung capacity, CPI composite physiologic index, CHF congestive heart failure (CHF), MI myocardial infarction, CAD coronary artery disease, PE pulmonary embolism, PH pulmonary hypertension. Hospitalizations include admissions at our institution for IPF-related complications

Table 2. Baseline treatment

IPF treatment	Anti-coagulation N=25	NO Anti-coagulation matched group N=25	NO Anti-coagulation N=72	p-value 0.037
Prednisone	4 (16%)	10 (42%)	26 (40%)	
Azathyoprine	15 (60%)	10 (42%)	19 (29%)	
Interferon gamma 1b	0	0	1 (1%)	
None	6 (24%)	4 (16%)	20 (30%)	

Values are N (%) or median (range). P-value is from the two comparator group: 25 treated patients and 97 untreated patients.

in progression free survival between the two groups (Fig. 2) (HR=2.7 [95% CI, 1.2 to 6.0; p=0.014]). After adjusting for age and any cardiovascular comorbidities the hazard ratio was 2.2 (95% CI, 0.96 to 5.1; p=0.063). Similar results are obtained using the matched group as comparator (HR=2.7, 95% CI: 1.2-6.5; p=0.023, Adjusted: HR=2.3, 95% CI: 0.96-5.7; p=0.060).

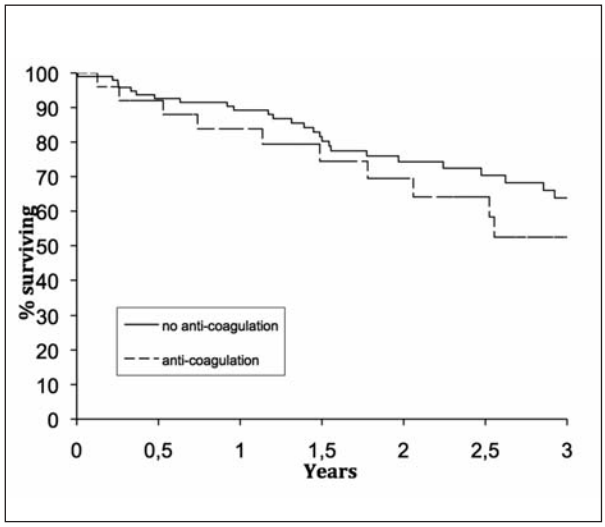

Fig. 1. Kaplan-Meier survival between the non-anticoagulant group and the anticoagulant group in regard to overall survival. Dashed line indicate the survival curve in the anticoagulant group. Solid line indicates the survival curve in the non-anticoagulant group. According to the Cox regression model, the hazard ratio for death was 3.4 (95% confidence interval (CI), 1.7 to 6.7; p <0.001) (Fig 1). After adjusting for age and any cardiovascular comorbidities the hazard ratio was 3.1 (95% confidence interval, 1.4 to 7.0; p=0.006)

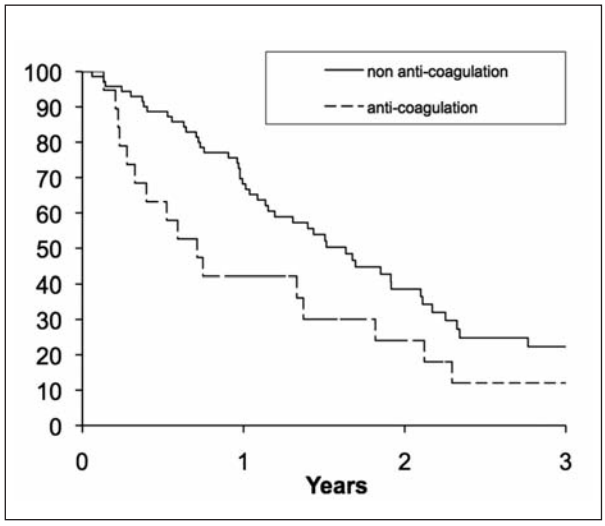

Fig. 2. Kaplan-Meier between the non-anticoagulant group and the anticoagulant group in regard to time to disease progression. Dashed line indicate the survival curve in the anticoagulant group. Solid line indicates the survival curve in the non-anticoagulant group. There was a significant difference in progression free survival between the two groups (Fig 2)(HR=2.7 (95% CI, 1.2 to 6.0; p=0.014). After adjusting for age and any cardiovascular comorbidities the hazard ratio was 2.2 (95% CI, 0.96 to 5.1; p=0.063).

Acute Exacerbation of IPF and pathology findings

We analyzed the incidence of acute exacerbations in a subgroup of 102 patients (23 treated with anticoagulant and 79 not treated) in which the follow-up data from the diagnosis until the date of last vital status assessment were sufficient to reliably asses AE. Among 23 patients experiencing AE-IPF five patients were in the anticoagulant group (5/23, 22%) and eighteen were in the non-anticoagulant group (18/79, 23%). In the matched untreated group we found 5 acute exacerbations (20%). Among the five patients with AE-IPF in the group treated with anticoagulants, 3 patients died of acute exacerbations (60%). Exactly the same AE-related mortality was observed in the matched untreated group. Of the eighteen patients with AE-IPF in the non-anticoagulant group, 12 died of acute exacerbation (66%).

Post mortem histological specimens were available in only one patient, a 63-year-old female non-smoker. Anticoagulant had been prescribed for pulmonary embolism that occurred four weeks before acute exacerbation of IPF that resulted in her death. At autopsy, histology showed an extensive diffuse alveolar damage mainly in exudative phase with hyaline membrane, superimposed on chronic background characterized by subpleural scarring and honeycombing. In the scarring area the artery showed a moderate intimal thickening with occasional acute in-situ thrombi. There were no features consistent with pulmonary embolism.

Anticoagulant therapy-related adverse events

Among the group of 25 treated patients, two (8%) had anticoagulant therapy-related complications. A 77-year-old man with cognitive disorder secondary to transient ischemic attacks, misinterpreted drug prescriptions and ingested both ticlopidine and warfarin for four months developing palpable cutaneous purpura all over the trunk and arms that required hospitalization and later resolved with appropriate management. The second case was a 70-year-old man who was admitted to the ICU for hemorrhagic shock due to massive intestinal bleeding caused by internal haemorrhoids while on anticoagulant therapy. This patient recovered after one month of hospitalization.

Discussion

In this retrospective cohort study of IPF patients seen in clinical practice we were not able to demonstrate any survival benefit from anticoagulant therapy. One and three-year survival was worse among patients on anticoagulant therapy compared to the non-anticoagulant group. Median time to disease progression was remarkably shorter in the anticoagulant group, but there was no difference in both the incidence of acute exacerbations and the number of deaths from acute exacerbations when compared to the non-anticoagulant group .

Two contradictory studies have been published evaluating the effect of anticoagulant therapy on the survival of patients with IPF (10, 12). The prospective study by Kubo and co-workers included 56 IPF patients admitted to five Japanese hospitals. Patients were randomly assigned to prednisolone alone or prednisolone plus anticoagulant therapy (oral warfarin or low-molecular-weight heparin). The authors showed that the mortality associated with acute exacerbations of IPF was significantly reduced in the anticoagulant group when compared to that in the non-anticoagulant group (18% versus 71%). These favorable results were questioned because there were study design weaknesses (the study was unblinded), possible misclassification bias, and were limited to patients who were hospitalized (therefore acutely ill or deteriorating patients). Furthermore, only nine cases were confirmed by surgical lung biopsy for the diagnosis of IPF, the power of the study was limited by differential dropout rates (excessive dropout in the anticoagulant group), failure to exclude pulmonary embolism as a potential cause of deterioration, and suboptimal documentation of the quality of anticoagulation during outpatient phases (1, 11). Conversely the large and well conducted prospective randomized double blind placebo controlled trial of warfarin therapy for IPF (ACE-IPF) showed that the use of warfarin was associated with an increased mortality when compared with placebo (adjusted HR 4.85; 95% confidence interval, 1.38-16.99) (12). Moreover this study showed a trend of higher all-causes hospitalizations, respiratory–related hospitalizations and acute exacerbation of IPF, suggesting that warfarin might worsen the respiratory status of IPF patients. However, the implications of this study is weakened by the selection bias of a population that does not reflect the spectrum of IPF patients we see in our clinical practice. First of all the study enrolled patients with severe disease (FVC % pred lower than 60% and DLco %pred. 34% in both treated and placebo arms); secondly patients who required anticoagulation for non-IPF related reasons were excluded. Our retrospective study shows that the IPF patients that we currently treat with warfarin for cardiovascular complication are older and carry a heavier burden of comorbidities compared to other IPF patients, but do not differ in pulmonary function and in the majority of cases (80%) are mild to moderate IPF, Despite the differences in population characteristics our outcome was strikingly similar to that reported by Noth and co-workers. One- and three-year survival were significantly worse in the group of patients on anticoagulant therapy. Although the patients on anticoagulant therapy carried a significantly increased burden of cardiovascular disorders such as heart failure, pulmonary embolism and pulmonary arterial hypertension, the worse survival in this group seemed unrelated to the increased burden of co-morbidities. This was shown by analysis of adjusted survival hazard ratio and adjusted progression-free survival and by sensitivity analysis that compared the treated group to a carefully matched untreated group. Survival adjusted for age and comorbidities was still significantly lower in the anticoagulant group and the same as previously reported, adjusted HR 4.8 (95% CI: 1.8-12.8). Moreover in both ACE trial and our study median time to disease progression was remarkably shorter in the anticoagulant arm, even after adjusting for age and comorbidities and even after comparing with the matched untreated group. These data strongly confirm the clinical observation by Noth and coworkers that respiratory worsening is the common feature contributing to mortality in warfarin treated patients. The biological explanation remains elusive. There is an interesting debate concerning the hypothesis that anticoagulation, beside warfarin, may still be indicated in IPF patients and other agents such as inhaled heparin might be investigated in the future (13). However mechanisms of IPF are largely unclear and based on current evidence we cannot exclude that many pathways observed in fibrogenesis related to increased procoagulant activity as well as suppression of the normal fibrinolytic activity may not be causative but rather a molecular response to

the disease. Therefore we can't exclude that antagonize them might worsen disease course.

In our study acute exacerbation of IPF was a common cause of hospitalization in both the anticoagulant group and the non-anticoagulant group. Number of deaths from AE-IPF in the two groups did not differ. This is different from what reported by Noth and collegues and might be in part explained by the two different settings of patients. Only a minority of our patients suffered from severe disease therefore we cannot address the incidence of acute exacerbation in this subgroup of patients. The incidence of adverse events related to anticoagulant treatment was high in our small cohort of treated patients (8%), one major bleeding (4%). The advanced age and the fragility of IPF patients, mainly due to coexistent comorbidities, in a real life setting may adversely affect patient compliance and increase the risk of drug-related complications.

We recognize several limitations of this retrospective analysis particularly the small number of patients in the anticoagulant group and differences in comorbidities with a significantly increased burden of comorbidities in the anticoagulant group. Nevertheless, this retrospective review afforded the opportunity to analyze the effect of anticoagulant therapy on patients with IPF seen in clinical practice in order to determine if previous data cautioning against the use anticoagulant treatment can be translated in a well-defined cohort of IPF patients in which warfarin was used for cardiovascular indications.

While acknowledging the limitations of this study, in particular the retrospective design, and the small number of treated patients, it does not appears that anticoagulant provide a meaningful survival benefit in IPF patients. Patients treated with anticoagulants experienced a worse survival and a shorter duration of time to disease progression. Based on this study we caution against the indiscriminate use of anticoagulants for IPF in current clinical practice.

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