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Colchicine, cyclophosphamide and prednisone in the treatment of mild-moderate idiopathic pulmonary fibrosis: comparison of three currently available therapeutic regimens

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Abstract. – *Study objectives:* **In this study we evaluated the role of three currently available therapeutic regimens in the treatment of early stages of idiopathic pulmonary fibrosis (IPF).**

Patients: **The study population consisted of 57 consecutive suspected individuals with IPF. Patients with interstitial pneumonias other than IPF and subjects with advanced disease or contraindication to therapy were excluded. We evaluated 30 subjects with mild-moderate IPF, homogeneous baseline characteristics and prognostic parameters that were assigned to 3 treatment regimens: group 1 (n = 11): prednisone 1 mg/kg/day; group 2 (n = 9): prednisone 0.5 mg/kg/day plus cyclophosphamide 100 mg/day; group 3 (n = 10): prednisone 0.5 mg/kg/day plus colchicine 1 mg/day.**

We analysed response to therapy by analysis of a clinical-radiographic-physiologic (CRP) score before treatment and at 6 months intervals for 18 months. Side effects and three years survival rate were also investigated.

Results: **Although our study was performed in a subset of patients with early disease's stages, these data showed that none of the regimens was able to interfere with IPF's course. However treatment with colchicine plus prednisone resulted in fewer side effects and re-evaluation parameters showed a significant decrease of dyspnoea ($p < 0.01$). No significant differences were observed in survival rate among the three groups.**

Conclusions: **None of the regimens analyzed was effective even in the treatment of the early stages of IPF. The association colchicine/corticosteroids could be considered a safe and not expensive regimen that may be used in the treatment of IPF, especially in patients who have experienced adverse effects from immunosuppressive agents, while waiting for newer therapeutic strategies.**

Key Words:

Colchicine, Prednisone, Cyclophosphamide, Idiopathic Pulmonary Fibrosis.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive inflammatory interstitial lung disease characterized by relative unresponsiveness to therapy and a poor prognosis with a median survival of 3 to 5 years after diagnosis[1-4].

The association of corticosteroids plus immunosuppressive agents is the recommended treatment but, because of the low rate of response and the high percentage of side effects, other therapeutic agents have been used in IPF treatment. The therapeutic role of these agents is not well defined yet and it is under investigation. Moreover few authors have investigated the efficacy of these treatments in early disease stage and most of the studies have analyzed patients with different baseline characteristics, unbalanced disease severity and prognostic factors[5-15].

In this study we compared efficacy, tolerability and impact on survival of three currently available therapeutic regimens (steroids alone, steroids plus cyclophosphamide, steroids plus

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colchicine) in mild-moderate IPF. After selection, we evaluated 30 patients with homogeneous clinical, radiographic and physiologic traits. For each regimen, response to therapy, adverse effects and survival rate were evaluated.

Materials and Methods

Study Population

From October 1998 to November 2002, we screened 57 consecutive unselected patients that were referred to Forlanini Hospital in Rome for suspected Idiopathic Pulmonary Fibrosis (IPF).

Diagnosic algorithm of IPF was based on clinical history, physical examination, lung function tests, histological findings, chest high resolution computed tomography (HRCT) according to the International Consensus Statement of American Thoracic Society criteria[15,16].

Open lung biopsies by Video-assisted thoracoscopy (VATS) or thoracotomy were performed in 8 patients, 25 subjects underwent transbronchial lung biopsies, all patients underwent bronchoalveolar lavage (BAL) and HRCT.

Among the 57 screened patients, 27 were excluded because they did not satisfy the inclusion criteria. Subjects with $DLCO_{sb} \leq 40\%$ of predicted, were considered to have advanced disease (Figure 1).

We examined 30 subjects with similar prognostic factors, baseline characteristics and mild moderate IPF assigned in an open study to 3 different regimens: group 1 (n = 11) prednisone, group 2 (n = 9) prednisone plus cyclophosphamide, group 3 (n = 10) prednisone plus colchicine.

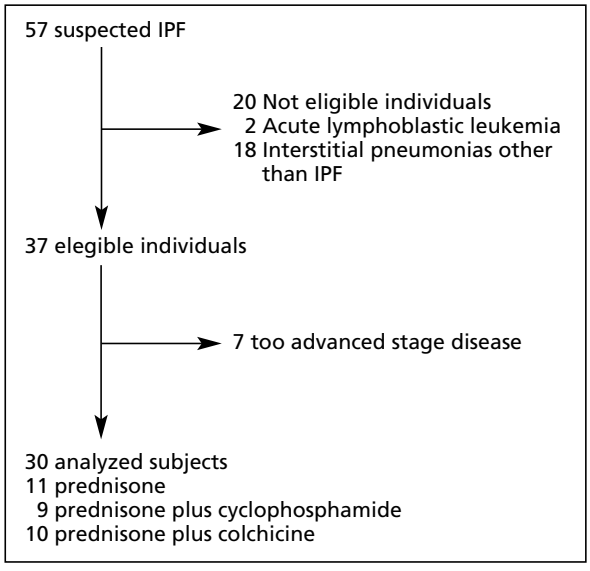

Figure 1. Flow-chart of patients analyzed in the study.

Clinical Radiological and Physiologic (CRP) Score

IPF severity was assesed for each patients using a previously developed clinical radiologic physiologic (CRP) scoring system[4,17]. Briefly we analyzed: level of dyspnea (0-20 points); spirometry (FVC 0-12 points, FEV_1 0-3); lung volumes (0-10); diffusion capacity for carbon monoxide (0-5); chest radiograph (0-10).

A global score was generated for each patient by the sum of scores assigned to the single variables.

We also measured oxygen saturation at rest by a pulse oximeter (Respironics, Marietta, GA, USA) and the percentage of saturated haemoglobin was recorded at each time point.

High Resolution Computed Tomography

All patients underwent chest HRCT, using an A-TOM XR 6000 apparatus (Ansaldo Elettronica Biomedicale, Genoa, Italy), with 1 mm thick sections at 10 mm intervals that were reconstructed using a high-spatial-frequency algorithm.

HRCT interstitial score was assessed by an independent radiologist (R. P.), according to Michaelson et al[18].

Briefly: 0 points were assigned for no HRCT evidence of interstitial disease; 1 point for interlobular septal thickening and no honeycombing; 2 points for honeycombing involving up to 25% of the lobe; 3 for honeycombing involving 25 to 49% of the lobe; 4 for honeycombing involving 50 to 75% of the lobe; 5 for honeycombing involving > 75% of the lobe.

Treatment Regimens and Follow-up

Group 1 (n =11) received prednisone 1 mg/kg/day for 4 weeks then 0.5 mg/kg/day for 2 months followed by a gradual reduction to a maintenance dose of 20 mg/day; group 2 (n = 9) received prednisone 0.5 mg/kg/day for 1 month, 0.25 mg/kg/day for 2 months following a reduction similar to previous group plus oral cyclophosphamide 100 mg/day and group 3 (n = 10) prednisone 0.5 mg/Kg/day (using same reduction protocol as for group 2) plus oral colchicine 1 mg/day.

CRP score, oxygen saturation and HRCT of each patient were evaluated by 2 independent physicians (F.F., E. L.B.) at the beginning of treatments and at 6 months intervals for 18 months.

Side effects was also investigated in each visit.

For survival analysis, time zero was considered as the initial visit (index visit).

Statistical Analysis

All statistical analyses were performed by using STATISTICA 5.1 software (StatSoft, Inc., Tulsa, OK, USA).

Data are shown as mean ± 1 SD. Because of data distribution, Kruskall Wallis -one-way variance analysis was used to compare the different groups. Analysis of survival was obtained using Kaplan-Meier product limit method, comparison between survival in different regimens was analyzed by Gehan's generalized Wilcoxon test modified for multiple sample analysis.

All analyses with a $p < 0.05$ were considered significant.

Results

Patient Characteristics

During the study period we identified 57 subjects with suspected IPF, 20 patients were excluded because of different diagnoses (acute lymphoblastic leukemia and interstitial pneumonia other than IPF). Seven subjects were excluded because of too advanced stage of disease. Therefore, thirty patients with mild/moderate IPF were included in the study (Figure 1).

Dyspnoea was observed in all subjects. Baseline pulmonary function tests showed a restrictive pattern.

We enrolled 17 men and 13 women, mean age was 65.4 ± 2.4. Average CRP score for the whole group was 28.6 ± 2.6 with a physiologic score of 16.9 ± 2.2, a clinical score of 6.4 ± 1.7, and a radiographic score of 5.1 ± 1.3.

Patients baseline characteristics are summarized in Table I. No significant differences were observed among the three groups. Mean duration of symptoms before the index visit was similar in all groups (11,8 ± 2,1 months).

Patients' follow-up

Patients' characteristics after 18 months follow up are described in Table II.

We compared the different variables between the three groups at follow-up and analyzed score differences from baseline to follow-up in each group. Comparison of dyspnoea among the three groups showed a significant improvement in patients of group 3. Two patients of group 1 (18%), one patient of group 2 (11%) and eight patients of group 3 (80%), showed a decrease of dyspnoea ($p = 0.001$). Analysis of score variations from baseline to follow-up revealed a significant difference in colchicine group (average –2.1 ± 1.3, 95% interval confidence –5.4 and 0.7) as compared with group 1 (average 3.1 ± 1.5, 95 % interval confidence –0.2 and 6.5) and group 2 (average 4.1 ± 1.9, 95% interval confidence –0.3 and 8.5) ($p = 0.03$).

Three subjects of group 1 (27%), one of group 2 (11%), and five of group 3 (50%), showed an improvement in SaO_2 at rest.

The evaluation of the other parameters investigated at follow-up (PFT, DL_{CO}, Chest x ray,

Table I. Baseline characteristics.

Characteristic	Group 1	Group 2	Group 3	*p* value
N°	11	09	10	N.S.
Age, yr	65 ± 2.3	65.1 ± 2.7	65.2 ± 3.2	N.S.
Female/Male	5/6	4/5	4/6	N.S.
CPR score	27.7 ± 2.5	5.3 ± 1.3	30.2 ± 3.4	N.S.
Dyspnea	5.7 ± 1.3	27.5 ± 2.5	8.4 ± 2.5	N.S.
Physiologic	16.4 ± 2.7	17.3 ± 2.5	17.1 ± 1.8	N.S.
Chest x ray	5.4 ± 0.6	5.1 ± 1	4.6 ± 0.8	N.S.
SaO_2%	93.4 ± 0.8	93.6 ± 1.3	94.1 ± 0.8	N.S.
HRCT (Interstitial Score)	2.8 ± 0.3	2.6 ± 0.6	2.4 ± 0.4	N.S.

N.S. = not significant

Table II. Comparison of patients characteristics at index visit and after 18 months.

Characteristic	Group 1	Group 2	Group 3	*p* value
CRP score				
Baseline	27.7 ± 2.5	27.5 ± 2.5	30.2 ± 3.4	N.S.
18 months	32,7 ± 2.8	33,7 ± 2.7	31 ± 3.1	
Dyspnea				
Baseline	5.7 ± 1.3	5.3 ± 1.3	8.4 ± 2.5	0.001
18 months	8.8 ± 1.2	8.9 ± 2	6.3 ± 2.2	
Physiologic				
Baseline	16.4 ± 2.7	18.9 ± 2.5	17.1 ± 1.8	N.S.
18 months	18.1 ± 2.4	18.4 ± 2.6	18.4 ± 2.3	
Chest x ray				
Baseline	5.4 ± 0.6	5.1 ± 1	4.6 ± 0.8	N.S.
18 months	6 ± 0.5	6.4 ± 1.2	6.3 ± 1.2	
SaO_2%				
Baseline	93.4 ± 0.8	94 ± 1.3	94.1 ± 0.8	N.S.
18 months	86.1 ± 0.7	91.9 ± 1.6	95 ± 0.6	
HRCT				
Baseline	2.8 ± 0.3	2.6 ± 0.6	2.4 ± 0.4	N.S.
18 months	3.6 ± 0.6	3.7 ± 0.8	3.1 ± 0.8	

N.S.= not significant.

HRCT) did not show any significant differences among the three groups.

Importantly, analysis of characteristics from baseline to follow-up for patients belonging the same group of treatment did not show significant differences for any of the groups analyzed.

Side Effects

Side effects were evaluated at each visit.

Hyperglycemia was observed in five patients of group 1 (45%) and two of group 3 (20%). No patients discontinued therapy because of diabetes mellitus. Mild gastrointestinal side effects (diarrhea, nausea) were observed using cyclophosphamide (22%) or colchicine (30%). Myelodepression was experienced in 3 patients treated with cyclophosphamide and therapy was discontinued in one subject (Table III).

Survival Rate

Survival analysis was performed after 3 years from index visit.

Four patients (36%) of group 1, four (44%) of group 2 and three (30 %) of group 3 died during the three years follow-up period. No significant differences in mortality rate were observed between male/female genders.

No significant differences were observed in survival ($p = 0.5$) among the three groups.

Table III. Adverse effects during treatment.

Adverse effects	Group 1	Group 2	Group 3	*p* value
Diabetes	5	0	2	0.002
Gastritis	3	2	3	N.S.
Hypertension	1	1	1	N.S.
Myelodepression	0	3	0	N.S.
Diarrhea	0	0	1	N.S.
Muscle cramps	0	0	1	N.S.
Vasculitis	0	0	1	N.S.
Neuronopathy	0	0	1	N.S.

N.S.= not significant.

Discussion

Idiopathic pulmonary fibrosis is a world wide progressive lung disease characterized by fatal outcome, irreversible distortion of lung architecture, respiratory failure and death in few years[15,19,20].

The observation that a chronic inflammatory state is responsible for the characteristic lung injuries, has leaded to the conventional therapeutic approach of IPF. Several clinical trials using anti-inflammatory agents (e.g. corticosteroids and/or immunosuppressive agents) have been investigated with controversial results and no anti-inflammatory agent has shown efficacy to halt or reverse IPF evolution[20-23]. Additionally, their use is associated with numerous and serious side effects. Until adequate studies will be able to define the best treatment for IPF, American Thoracic Society committee has suggested a combined therapy with corticosteroids and immunosuppressive agents (cyclophosphamide, azathioprine)[15].

Colchicine is an antifibrotic agent, which suppresses the release of macrophage-derived growth factor (MDGF) and fibronectine by alveolar macrophages *in vitro.* The results of trials using this agent are controversial but side effects attributed to colchicine are rarely severe, not causing a discontinuation of therapy[5,7].

New anti-fibrotic agents (e.g. pirfenidone) have been recently used with interesting results in advanced IPF not responding to conventional anti-inflammatory therapy[24-26].

The use of gamma-1b interferon has been recently investigated in IPF, with controversial results[27-31].

Lung transplant is considered an important therapeutic option but,unfortunately, only few selected subjects could undergo surgery and the rate of complications is still high[21,32,33].

Optimal therapy is still not clear and under debate; nowadays there is a lack of clinical evidences that current therapies significantly improve quality of life or survival time. Many studies investigating effectiveness of IPF therapy have faced important limits. Most of them were uncontrolled, with heterogeneous, unbalanced groups of patients, presence of other systemic disease that influence therapy and prognosis[34-36].

Some clinical trials have tested the efficacy of new medications on individuals not responsive to corticosteroids or with an advanced IPF stage[9,34].

In previous studies worse survival and response to therapy was observed in subjects with older age, lower pretreatment vital capacity, DL_{CO} and SaO_2 at rest and a delayed beginning of treatment[4].

Because of the lack of response in advanced IPF, it could be important to investigate a possible impact of therapy in early stage of disease avoiding any misleading biases. In our study we investigated the effect of therapy on mild-moderate stage of IPF which should be more responsive to therapy. To accomplish this we evaluated 30 consecutive IPF proven patients that were referred to our division, excluding subjects with too advanced stage of disease, or with clinical conditions (e.g. diabetes mellitus, peptic ulcer, cardiac diseases, bone marrow dysfunctions), which could interfere with the evaluation of therapy's side effects. Analysis of re-evaluation parameters, showed that a significant number of subjects undergoing treatment with corticosteroids and colchicine experienced an improvement of dyspnoea compared to the other treatments.

It is important to underline that, although we found a significant decrease in dyspnoea in group 3, there weren't any significant differences in CPR global score.

On the other hand the decrease of dyspnoea which is considered the most disabling symptom for IPF patients is associated with a better quality of life[15].

Accordingly to literature, treatment with colchicine resulted in fewer serious side effects (mild hyperglycemia or diarrhoea) and did not cause discontinuation of therapy[2,5,6].

Analyses of three years survival rate and of the other parameters used in monitoring IPF clinical course, showed that the regimens analysed were unable to interfere with lung deterioration.

Our study had some limitations. First it was performed in 1 center, not allowing to rule out selection biases. Second, we enrolled a limited number of patients. We believe that multicenter studies analyzing a larger number of subjects are needed to confirm our data. Third it is an open study not random.

In summary our findings confirmed previous reports, showing that none of the regimens studied was able to interfere with IPF course even in early disease's stages. Among the 3 regimens a significant number of patients treated with colchicine plus prednisone experienced an improvement in dyspnoea and fewer serious side effects.

We conclude that the association prednisone plus colchicine is a safe and not expensive therapy that could be utilized as a valid option in IPF treatments in patients who have experienced adverse effects from high of corticosteroids dosage and from cyclophosphamide, while waiting for new, not cost consuming and more effective therapeutic strategies.

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