Colchicine, D-Penicillamine, and Prednisone in the Treatment of Idiopathic Pulmonary Fibrosis*

A Controlled Clinical Trial

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**Study objective:** We compared the long-term efficacy of the combination of colchicine and/or D-penicillamine with prednisone, in comparison to prednisone alone in patients with idiopathic pulmonary fibrosis (IPF).

**Design:** Nonrandomized prospective study in patients with IPF confirmed by biopsy specimen.

**Setting:** National Institute of Respiratory Diseases, Mexico.

**Patients:** Fifty-six IPF patients were included in this study. Patients received either colchicine/prednisone (n=19), D-penicillamine/prednisone (n=11), D-penicillamine/colchicine/prednisone (n=11), or prednisone alone (n=15). Prednisone therapy was started at 1.0 mg/kg/d for 1 month followed by a biweekly taper to a maintenance dose of 15 mg/d. Colchicine was administered at a daily dose of 1.0 mg, and D-penicillamine was given at a daily dose of 600 mg.

**Measurements and results:** Response to therapy was assessed by changes in lung function test results as measured by total and vital lung capacities, arterial blood gas analysis at rest breathing room air, and survival. No significant differences either in lung mechanics or in arterial gases were found in any group relative to the baseline measurement. Thirteen of the 56 patients died during the first 2 years, and 29 were dead at 5 years follow-up. Comparison of survival curves by Cox regression model showed no statistically significant difference among the four groups. Known side effects attributable to prednisone were more common and severe than those attributable to the other drugs.

**Conclusions:** Our results suggest that neither colchicine nor D-penicillamine modified the progressive course of prednisone-treated IPF, and that the search for new drugs is imperative. (CHEST 1998; 114:507–512)

**Abbreviations:** IPF=idiopathic pulmonary fibrosis; PSS=progressive systemic sclerosis; TLC=total lung capacity

**Key words:** idiopathic pulmonary fibrosis; fibrosing alveolitis; colchicine; D-penicillamine; prednisone corticosteroids

Idiopathic pulmonary fibrosis (IPF) is a chronic diffuse interstitial and intra-alveolar fibrosing inflammatory disease of unknown etiology that continues to represent an important therapeutic problem. Although the clinical course is variable, the disease is usually progressive and it is considered a highly lethal lung disease. Histopathologic findings include an inflammatory and a fibrotic component, with temporal and spatial inhomogeneity, and the cellular or the fibrotic predominance, when diagnosis is made, is considered the main prognostic factor.

Corticosteroids as well as other immunosuppressive or cytotoxic drugs are currently used with poor and transient response, or without success at all. Additionally, other pharmacologic approaches have been attempted, including colchicine, D-penicillamine, and cyclosporine, but most studies have been retrospective or uncontrolled trials. Particularly colchicine has created encouraging expectation, and a recent study comparing 22 patients who received colchicine with 22 historical patients who were given prednisone suggested that this drug may be of benefit in the treatment of IPF. Colchicine is an inhibitor of collagen synthesis and secretion, promotes collagenolytic activity, and suppresses the release of some fibroblast growth factors by alveolar macrophages, all of these putative antifibrotic

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properties support the notion that this drug could be useful as a therapeutic agent in lung fibrotic disorders. D-penicillamine may inhibit collagen accumulation through disruption of several posttranscriptional steps of collagen synthesis, including crosslinking, and it has been used in fibrotic lung disease associated with progressive systemic sclerosis (PSS) with clinical and functional improvement. Interestingly, in the study of Steen et al., therapy with colchicine or immunosuppressive agents in PSS was not associated with similar improvement. However, this retrospective study has not been confirmed by a prospective, randomized study either in this disorder or in IPF.

In 1983, we initiated a prospective clinical trial to compare the effect of combined colchicine/prednisone, D-penicillamine/prednisone, and D-penicillamine/collchicine/prednisone with prednisone alone in the treatment of IPF. The question of whether the combinations of steroids with colchicine or D-penicillamine offer additional beneficial effects when compared with prednisone alone was the subject of the present research.

**Materials and Methods**

**Study Population**

Fifty-six adult patients with clinical, radiologic, and functional features of interstitial lung disease and histologically proven diagnosis of IPF were enrolled in this prospective study. The patients were seen at the National Institute of Respiratory Diseases in Mexico City between 1983 and 1990, and the protocol was approved by the corresponding Scientific and Ethical Committees. Diagnosis of IPF was suspected in patients with progressive dyspnea, diffuse reticulonodular infiltrates on chest radiograph, bibasilar crackles, digital clubbing, decrease in FVC and PaO2, and no evidence of systemic disease or environmental exposure. The morphologic diagnosis of IPF, which was based on typical microscopic findings, included patchy alveolar septal fibrosis and interstitial inflammation consisting mostly of mononuclear cells but also of neutrophils and eosinophils; a variable macrophage accumulation was observed in the alveolar spaces as was the cuboidalization of the alveolar epithelium. Biopsy specimens lacked granulomas, vasculitis, microorganisms, and inorganic material by polarized light microscopy. The lung samples were taken by open lung biopsy, usually 1 week after hospital admission. None of the patients had been treated with immunosuppressive drugs at the time of biopsy. Lung biopsy tissue was obtained from two different sites from the middle lobe of the right lung or from the inferior lobe of the left lung, fixed immediately with 10% formaldehyde, and handled in identical conditions.

**Semi-quantitative Histologic Assessment**

The percentage of fibrosis and inflammation in lung samples was analyzed as described elsewhere. Briefly, the assessment was done on the slide scanned completely in zigzag fashion, first at X32 and then at X125 magnification. In all cases, four slides, two of them stained with Masson’s trichrome and two with hematoxylin-eosin, were analyzed. The percentage of fibrosis and inflammation was expressed in multiples of 10. Intraobserver reproducibility was evaluated using the weighted kappa statistic and was of 0.58±0.13 (p<0.0001).

**Pulmonary Function Tests**

Spirometry was performed using electronic integration of a pneumotachometer signal (Erich Jaeger GmbH & CoKG, Wurzburg, Federal Republic of Germany). Three acceptable FVC maneuvers were obtained from each patient and the best FVC and FVC were chosen. Total lung capacity (TLC) and residual volume were derived from functional residual capacity that was measured in a constant volume plethysmograph (Jaeger Bodytest; Erich Jaeger GmbH & CoKG). Spirometric measurements and the subdivisions of lung volume were expressed as percent of predicted using the reference equations by Quanjer.11 PaO2 and PaCO2 were also recorded.

**Treatment Protocol and Follow-up**

Patients were assigned into four groups: group 1 (n=15)—prednisone; group 2 (n=19)—prednisone and colchicine; group 3 (n=11)—prednisone plus D-penicillamine; and group 4 (n=11)—prednisone, colchicine, and D-penicillamine. In all groups, prednisone was given at a initial dose of 1.0 mg/kg/d for 1 month followed by a reduction of 5 mg/d every 2 weeks until a maintenance dose of 15 to 20 mg/d was reached. The four groups received oral prednisone according to an identical protocol. Colchicine was administered at a daily dose of 1.0 mg, and D-penicillamine was given at a daily dose of 600 mg. In all groups, treatment was prolonged during all the time of follow-up. Patients were recruited prospectively during 8 years and followed up during at least 5 years. Treatments were concurrent and the physicians responsible for follow-up were the same. Patients were evaluated 1 month after starting treatment, then at 3 months, and subsequently at 3-month intervals for 2 years and 6-month intervals thereafter unless more often was clinically indicated. Response to therapy was assessed by changes in dyspnea score (dyspnea at exercise, 1: slight; 2: moderate; 3: severe; 4: dyspnea at rest), and in lung function test results as measured by TLC and FVC, and arterial blood gas analysis at rest breathing room air. Evidence of adverse effects was recorded in each visit.

**Statistical Analyses**

Data were expressed as means±SD. Unpaired Student’s t test was used to analyze the relationship between percentage of fibrosis and mortality. Survival was assessed by the method described by Kaplan and Meier and the Cox proportional hazards regression model. Independent predictors for the models were age, gender, and treatment given. Software (SURVIVAL; Systat Inc, Evanston, Ill) was used for stepwise regression for proportional hazards model.

**Results**

Baseline characteristics of the four groups are summarized in Table 1. Dyspnea score and pulmonary function test results were comparable among the groups. Younger patients were located in group 4.
who received prednisone, colchicine, and D-penicillamine when compared with the prednisone and prednisone plus colchicine groups (p<0.05). Five patients were unavailable during the 5-year follow-up. The end points examined for therapeutic outcome were measurable change in dyspnea score, lung function at 1 and 2 years, and survival. No significant changes were observed in dyspnea score.

Including the initial measurement, pulmonary function tests were obtained at least three times during the follow-up in survivors. Results of FVC, TLC, PaO₂, and PaCO₂ after 2 years of treatment are shown in Table 2. Although a trend for improvement in FVC was observed in three groups after 2 years of follow-up, no significant differences either in lung mechanics or in arterial gases were found in any group relative to the baseline measurement. In addition, when initial and 2-year follow-up lung function tests were examined only in survivors, significant differences were not found (not shown). Thirteen of the 56 patients included in the study died during the first 2 years, and 29 were dead at 5 years of follow-up. The survival curves of the four groups are presented in Figure 1. Comparison of survival in the four treatment groups by Cox regression model showed no statistically significant difference among them.

Women displayed higher mortality than men. Thus, at the 5-year follow-up, 23 of 36 female vs 6 of 20 male had died (p<0.02). Age was not a prognostic factor for these patients, and both young and older patients’ conditions worsened, and some even died without significant differences.

Evolution time before diagnosis was 38±34 months in group 1, 16±13 months in group 2, 35±25 months in group 3, and 14±13 months in group 4 (p=0.09). No significant association between evolution time before diagnosis and survival was found.

Using a semiquantitative histologic approach, the percentage of fibrosis in the lung samples varied from 10 to 70%, and there was no statistical difference among the four groups. However, independently of treatment scheme, survivors showed a significantly lower percentage of lung fibrosis in comparison to patients who died (37±17 vs 54±16; p=0.002).

Adverse effects attributed to prednisone were observed in 90% of the patients and included increased appetite and weight gain (90%), gastritis and/or peptic ulcer disease (28%), hyperglycemia (9%), depression (5%), osteoporosis (5%), and muscular weakness (3%). No side effects other than mild diarrhea (10% of the patients) were noted in patients who used colchicine. Probably due to the low doses used, no side effects attributable to D-penicillamine were observed. In general, patients complained more of the known adverse effects of prednisone than those observed with the other drugs.

**Table 1—Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>P</th>
<th>P+C</th>
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<tr>
<td>n</td>
<td>15</td>
<td>19</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Age, yr</td>
<td>55±10</td>
<td>55±15</td>
<td>49±18</td>
<td>46±11</td>
</tr>
<tr>
<td>Sex, F/M</td>
<td>12/3</td>
<td>10/9</td>
<td>6/5</td>
<td>8/0</td>
</tr>
<tr>
<td>Evolution, mo</td>
<td>38±34</td>
<td>16±13</td>
<td>35±25</td>
<td>14±13</td>
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<tr>
<td>Dyspnea</td>
<td>2.9±0.9</td>
<td>2.5±1.1</td>
<td>2.7±0.7</td>
<td>2.2±0.6</td>
</tr>
<tr>
<td>FVC%</td>
<td>41±17</td>
<td>44±22</td>
<td>44±23</td>
<td>26±5</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>45±7</td>
<td>44±11</td>
<td>46±12</td>
<td>48±11</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td>35±8</td>
<td>33±5</td>
<td>35±5</td>
<td>35±6</td>
</tr>
</tbody>
</table>

*P=prednisone; C=colchicine; DP=D-penicillamine. The study was done in Mexico City at 2,240 m over the sea level at a mean barometric pressure of 593 mm Hg. FVC%=FVC as percent of predicted.

**Table 2—Pulmonary Function Before and After 2 Years of Therapy**

<table>
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<tr>
<th></th>
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<tbody>
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<td>FVC%</td>
<td>41±17</td>
<td>44±22</td>
<td>27±11</td>
<td>35±16</td>
</tr>
<tr>
<td>Baseline</td>
<td>51±18</td>
<td>57±17</td>
<td>51±18</td>
<td>55±18</td>
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<tr>
<td>2 yr</td>
<td>64±20</td>
<td>67±7</td>
<td>64±33</td>
<td>ND</td>
</tr>
<tr>
<td>TLC%</td>
<td>63±13</td>
<td>66±24</td>
<td>56±6</td>
<td>ND</td>
</tr>
<tr>
<td>PaO₂, mm Hg</td>
<td>45±7</td>
<td>44±11</td>
<td>46±11</td>
<td>48±11</td>
</tr>
<tr>
<td>Baseline</td>
<td>45±8</td>
<td>40±6</td>
<td>45±8</td>
<td>42±2</td>
</tr>
<tr>
<td>2 yr</td>
<td>35±8</td>
<td>33±5</td>
<td>35±5</td>
<td>35±6</td>
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<tr>
<td>PaCO₂, mm Hg</td>
<td>32±4</td>
<td>37±4</td>
<td>39±17</td>
<td>44±7</td>
</tr>
</tbody>
</table>

*FVC% and TLC%=FVC and TLC as percent of predicted. ND=Not done. See Table 1 footnotes for expansion of other abbreviations.

**Discussion**

IPF represents a prototype of an aggressive and usually progressive interstitial lung disease that continues being a therapeutic problem for the clinician. Corticosteroids are currently the recommended pharmacologic therapy, mainly with the rationale of stabilizing or preventing disease progression by suppression of the chronic inflammation. However, their long-term benefits are questionable. Thus, although a number of patients treated with corticosteroids feel better, results of objective functional tests confirm this improvement in only 10 to 30%. Moreover, Izumi et al found that untreated patients with IPF followed up to 10 years after diagnosis exhibited similar behavior, or even did somewhat better, than
patients treated with corticosteroids. This finding is important because the natural history of untreated IPF patients has not been elucidated, and although one cannot reliably predict the clinical course of a given patient, nearly all of them are usually treated with corticosteroids. Additionally, high-dose therapy with corticosteroids is associated with numerous and potentially serious side effects. Because of this, and by the relatively low clinical response rate, other agents, mostly cytotoxic drugs like cyclophosphamide and azathioprine, have been assayed but also with marginal, if any, short-term favorable response.\textsuperscript{15,16}

The D-isomer of penicillamine has been proposed as a putative antifibrotic drug. It appears to affect collagen turnover at several points, mostly by blocking aldehyde groups involved in the intermolecular and intramolecular cross-linkages of mature collagen.\textsuperscript{17} In addition, D-penicillamine may also contribute to decrease abnormal collagen accumulation by inhibiting collagen biosynthesis.\textsuperscript{18}

D-penicillamine has demonstrated a beneficial effect in the treatment of interstitial lung disease associated with PSS,\textsuperscript{19} and it has been used to prevent the exaggerated collagen deposit in several models of pulmonary fibrosis.\textsuperscript{19,20} In IPF, however, it has been used only in a few patients, usually in uncontrolled trials, and without a clear significant clinical or functional improvement.\textsuperscript{21,22}

Colchicine has been successfully used in the treatment of human liver fibrosis and importantly, it mediates its effect at doses that are tolerated in vivo.\textsuperscript{23} The drug binds microtubular proteins interrupting cellular mitosis, and thus inhibits collagen biosynthesis. Additionally, it stimulates collagenase activity and inhibits the release of some fibroblast growth and chemotactic factors, and then limits fibroblast expansion in the lung parenchyma.\textsuperscript{7-9,24} All these effects, and the low incidence of ordinarily moderate side effects, make this drug an excellent candidate for the therapy of human fibrotic disorders.

In this context, colchicine, as either a single drug or combined with corticosteroids, has claimed to be at least as effective as immunosuppressive agents in the treatment of IPF, but studies have been retrospective, uncontrolled, and with short follow-up.\textsuperscript{6,25} With these precedents, we designed this project to test the possible usefulness of the combination of colchicine or/and D-penicillamine with prednisone in the prognosis of IPF patients.

It is important to emphasize that the design of

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure1.png}
\caption{Kaplan-Meier estimate of survival in a cohort of 156 IPF patients separated by treatment. There were no significant differences between subgroups.}
\end{figure}
therapeutic trials in patients with IPF faces several important problems. Although the disease is usually a lethal condition, the conditions of individual patients may initially improve with corticosteroids or cytotoxic drugs. Therefore, although a recent study suggested that as a group patients with steroids have the same survival rate as those who did not receive therapy, at the time that our study started, it was unethical to include a placebo group. The study also lacks the random allocation of the patients that could explain some of the differences among groups. Additionally, the number of subjects is also relatively reduced and therefore we cannot rule out differences in improvements offered by the tested treatments. Despite these shortcomings, we consider that the data are important and offer valuable information.

In general, the results of this study strongly suggest that neither colchicine nor D-penicillamine contributed to a better clinical response compared with prednisone alone. This finding could be at least partially explained by the advanced stage of the disease in most of our patients at the initial evaluation (average of FVC<50%; average of PaO₂<50 mm Hg at 2,240-m altitude). Thus, for example, these initial functional test results are markedly worse than those displayed by the patients in the Mayo Clinic Rochester study. Therefore, we cannot rule out that colchicine or D-penicillamine might have some beneficial effect on IPF patients if they are treated in early stages of the disease.

In addition to the presence of advanced lung disease at the time of diagnosis, hypoxemia due to altitude is another likely explanation for the excess mortality. The patients of this study used to live in Mexico City located at 2,240-m altitude. In this context, we have previously found that the survival in patients with chronic hypersensitivity pneumonitis and IPF living in the valley of Mexico is considerably worse than patients reported in developed countries at sea level. In addition, our patients cannot have long-term home oxygen therapy due to its cost.

Although we could not find differences in mortality or other indicators among treatments, we did easily for adverse effects by individual drugs. As expected, the known side effects of prednisone were more serious, whereas colchicine and D-penicillamine were well tolerated.

In summary, our findings suggest that prednisone alone does not prevent a progressive decline in the natural course of IPF, and did not support the assumption that colchicine or D-penicillamine may add some beneficial effect. Further studies with large numbers of patients and in earlier stages of the disease are necessary to have stronger evidence to make clinical recommendations. Nevertheless, the search for new drugs capable of modifying the natural history of the fibrotic lung disorders is imperative.

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