Limitations of Corticosteroids and Cytotoxic Agents in Treating Idiopathic Pulmonary Fibrosis

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Abstract: Although anti-inflammatory drugs such as steroids and cytotoxic agents have been used to treat idiopathic pulmonary fibrosis (IPF), these conventional anti-inflammatory therapies do not improve its outcome, probably because fibrosis is not preceded or provoked by alveolitis. A new therapeutic strategy aimed at suppressing abnormal fibroproliferative responses needs to be verified in Japanese patients with IPF.

Key words: Idiopathic pulmonary fibrosis; Steroid therapy; Cytotoxic agents; Anti-Fibrotic agents; Immune modulators

Introduction

Among the various types of interstitial pneumonias, alteration of the natural history of idiopathic pulmonary fibrosis (IPF) by therapeutic interventions has met with limited success, resulting in an extremely poor prognosis. This paper outlines issues involved in the treatment of IPF.

Problems with Previous Studies on the Treatment of IPF

Idiopathic pulmonary fibrosis (IPF) is a type of idiopathic interstitial pneumonia that progresses to widespread interstitial fibrosis and irreversible destruction of lung architecture. IPF histologically exhibits a patchy interstitial scarring process that emanates from the subpleural areas and septa, and also is characterized by both the presence of aggregates of fibroblasts, termed fibroblastic foci, and honeycomb formation of lung (Table 1).

The treatment of IPF is frustrating because no established therapeutic regimen supported by convincing evidence currently exists. Problems found in studies on the treatment of IPF (Table 1) include (1) a lack of randomized
placebo-controlled trials demonstrating the significance of steroids and immunosuppressants such as cyclophosphamide, (2) insufficient numbers of patients studied to date, and (3) confusion with nonspecific interstitial pneumonia (NSIP), i.e., prior to the introduction of the concept of NSIP in 1994, some cases of NSIP were confused with IPF, leading to overestimation of the effects of steroids or immunosuppressants, partly because those with NSIP that is more responsive to steroids have a significantly better outcome than those with IPF. This confusion is likely to remain a problem, since some cases of NSIP can not be differentiated from IPF. Key features in the histologic diagnosis of IPF include the presence of aggregates of actively proliferating fibroblasts and honeycomb lung. However, no consensus currently exists among pathologists as to the degree to which the findings of these features are acceptable when making a diagnosis of NSIP. These problems have led researchers to point out various drawbacks in previous studies. As noted above, the greatest drawback is that no randomized controlled study has been carried out in Japan to indicate the efficacy of steroid and immunosuppressant therapies.

Table 1  
Idiopathic Pulmonary Fibrosis and Problems in Clinical Studies

<table>
<thead>
<tr>
<th>Features of idiopathic pulmonary fibrosis</th>
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<tbody>
<tr>
<td>• One type of idiopathic interstitial pneumonia</td>
</tr>
<tr>
<td>• Patchy distribution of variegated lesions from inflammation to scarring</td>
</tr>
<tr>
<td>• Aggregates of fibroblasts</td>
</tr>
<tr>
<td>• Destruction of lung architecture that emanates from subpleural areas with honeycomb change</td>
</tr>
<tr>
<td>• Progressive nature</td>
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</table>

<table>
<thead>
<tr>
<th>Problems with therapeutic studies of idiopathic pulmonary fibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Insufficient investigation using randomized placebo-controlled studies</td>
</tr>
<tr>
<td>• Inadequate numbers of patients in case-control studies</td>
</tr>
<tr>
<td>• Possibility of misdiagnosis of nonspecific interstitial pneumonia (NSIP) as IPF</td>
</tr>
</tbody>
</table>

**Relevance of Evidence-Based Medicine from the U.S. and Europe to Japanese Patients with IPF**

The concept of evidence-based medicine (EBM) proposed in the 1990s has had a revolutionary effect on the practice of medical care.¹ A critical question posed by EBM, however, is that of how results reported in the literature should be applied to actual patients. Nevertheless, the prevailing trend is for emphasis to be placed on the evidence itself. An important issue to be aware of is whether the characteristics of the population presented in the literature are the same as those of the patients who are actually being treated. In other words, to what extent are results reported in the literature relevant to the individual patients that we see.²

From this point of view, it would be desirable for a randomized controlled study to be carried out in Japan, in the event that race-related differences might be present. For instance, there is room for discussion as to whether steroid therapy that is efficacious against certain diseases in Caucasians is also of benefit in Japanese people, who generally have less glucose tolerance. It is also unclear whether the relative ratios of the molecular species of the drug-metabolizing enzyme cytochrome P-450 are the same among patients of different races.

**Patients with IPF Amenable to Treatment**

What types of patients are amenable to treatment once a diagnosis of IPF has been established? The answer to this question varies, as there are differences of opinion on how to determine the propriety of treatment for individual patients. Because of the current lack of effective treatment based on definitive evidence, one suggestion is that patients be followed throughout the course of their illness and treatment be considered when a downhill course is observed.
On the other hand, as noted in the Consensus Statement by the American Thoracic Society (ATS) and the European Respiratory Society (ERS), the view is held by some that treatment should be performed in all patients unless there are contraindications to therapy, because IPF has a poor prognosis. The statement also suggested that the response rate might increase among patients who receive treatment in an early stage of the disease. 3)

In various institutes, including ours, the natural course of patients with IPF is usually followed after the diagnosis has been established. However, treatment is considered in cases such as those listed in Table 2. 4)

Table 2 Patients with Idiopathic Pulmonary Fibrosis Indicated for Treatment

1. Patients who have worsening clinical findings or findings on imaging.
2. Patients who have a 20% or higher proportion of lymphocytes in bronchoalveolar lavage fluid.
3. Patients in whom a diagnosis of collagen disease has not been established but is suggested by clinical symptoms and blood test data.
4. Patients whose condition is difficult to distinguish from nonspecific interstitial pneumonia (NSIP).
5. Patients in whom histologic examination has revealed areas showing histologic features other than those of usual interstitial pneumonia (UIP).

Table 3 Considerations Regarding Indications of Treatment

1. Since idiopathic pulmonary fibrosis has a poor prognosis, treatment should be given if it outweighs treatment-related complications.
2. Given the limited success of current treatments, patients in the early stage of IPF may respond better to treatment.
3. Caution is necessary in patients with the following characteristics, which are liable to lead to treatment-related complications: age over 70 years, extreme obesity, concomitant major illness such as cardiac disease, diabetes mellitus, or osteoporosis, severe impairment in pulmonary function, end-stage honeycomb lung.
4. Prednisolone at a dose of 0.5 mg/kg/day should be given for 4 weeks, followed by a reduced dose of 0.25 mg/kg/day for 8 weeks, then tapering to 0.125 mg/kg/day. At the same time, cyclophosphamide (2 mg/kg/day) or azathioprine (2–3 mg/kg/day) should be combined.

(From the International Consensus Statement. Am J Respir Crit Care Med 2000; 161: 646.)

Treatment of IPF Patients

As indicated in Table 3, particular attention
is required when the patient has certain characteristics that are vulnerable to treatment-related complications, i.e., age over 70 years, extreme obesity, cardiac disease or diabetes mellitus, osteoporosis, severe impairment in pulmonary function, and end-stage honeycomb lung. At present, the recommended treatment is oral prednisone [not available on the Japanese market; almost equivalent to prednisolone (Predonine®)] at a daily dose of 0.5 mg/kg combined with cyclophosphamide (Endoxan®) or azathioprine (Imuran®) at a daily dose of 2 mg/kg. The background for this recommendation includes data such as those presented in Table 4. The response rate for steroid monotherapy in previous case studies has generally ranged from 10–20%.

Steroids are considered to exert their effects through inhibition of the production of monocyte chemoattractant protein-1 (MCP-1) from bronchial epithelia and activated macrophages; inhibition of interleukin-8 (IL-8), which is important for the migration and activation of neutrophils; and inhibition of the production of various cytokines from activated T lymphocytes. In clinical cases, however, the efficacy of steroid monotherapy unfortunately has not met our expectations. It is reported that patients given no treatment sometimes achieve better survival rates than those who are given treatment but do not respond to it (see, for example, the report of Turner-Warwick, 1980).

### Table 4  Summary of Clinical Studies of Idiopathic Interstitial Pneumonia and the Results of Treatment

<table>
<thead>
<tr>
<th>Year</th>
<th>Author</th>
<th>No. of subjects</th>
<th>No. of patients given steroid therapy</th>
<th>Response rate (No. of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960</td>
<td>Scadding</td>
<td>26</td>
<td>12</td>
<td>8.3% (1) Slight improvement in 4 cases</td>
</tr>
<tr>
<td>1964</td>
<td>Livingstone</td>
<td>45</td>
<td>31</td>
<td>6.5% (2) Slight improvement in 5 cases</td>
</tr>
<tr>
<td>1965</td>
<td>Stack</td>
<td>42</td>
<td>31</td>
<td>13% (4)</td>
</tr>
<tr>
<td>1978</td>
<td>Carrington</td>
<td>53</td>
<td>26</td>
<td>11.5% (3)</td>
</tr>
<tr>
<td>1978</td>
<td>Winterbauer</td>
<td>20</td>
<td>20</td>
<td>60% (12)</td>
</tr>
<tr>
<td>1980</td>
<td>Turner-Warwick</td>
<td>220</td>
<td>Four-year survivors were observed in 18% of ineffective cases and 40% of untreated cases</td>
<td></td>
</tr>
<tr>
<td>1983</td>
<td>Tukiainen</td>
<td>113</td>
<td>100</td>
<td>30.3% (in 4 years)</td>
</tr>
<tr>
<td>1987</td>
<td>Guerry-Force</td>
<td>18</td>
<td>14</td>
<td>14.3% (2)</td>
</tr>
<tr>
<td>1987</td>
<td>Watters</td>
<td>26</td>
<td>37%</td>
<td>(7/19)</td>
</tr>
</tbody>
</table>

P: prednisone or prednisolone, C: cyclophosphamide, A: azathioprine.

### Table 5  Double-Blind Studies on Treatment of Idiopathic Interstitial Pneumonia

  - 22 patients received prednisolone monotherapy (initially 60 mg, reduced to 20 mg every other day).
  - 21 patients received cyclophosphamide (100–120 mg) and prednisolone (20 mg every other day).
  - The disease was refractory to both therapies, but prognosis was better in the latter group. (3-year survival, 55% vs. 86%)
  - 13 patients received prednisone monotherapy (1.5 mg/kg/day for 2 weeks, followed by 20 mg/day).
  - 14 patients received azathioprine (3 mg/kg/day) and prednisone (1.5 mg/kg/day for 2 weeks, followed by 20 mg/day).
  - After adjusting for age, results were significantly better in the latter group (9-year survival, 23% vs. 57%).
Double-blind studies comparing steroid monotherapy and combined steroid and immunosuppressant therapy have revealed that the combined therapy is more effective (Table 5). More specifically, Turner-Warwick’s group compared 22 patients treated with prednisolone monotherapy (initial dose 60 mg, reduced by 5 mg every week, to a regimen of 20 mg every other day) with 21 patients given a combination of cyclophosphamide (100–120 mg) and prednisolone (20 mg every other day). The results showed a tendency to better prognosis with the latter therapy, although the disease was refractory in both groups. The 3-year survival rate was reported to be 55% in the prednisolone monotherapy group while it was 86% in the combined therapy group.

Raghu et al. compared prednisone monotherapy (1.5 mg/kg/day for 2 weeks, followed by a 20 mg/day maintenance dose) in 13 patients with combined therapy consisting of azathioprine (3 mg/kg/day) and prednisone in 14 patients. After adjusting for age, prognosis was better with the combined steroid and immunosuppressant therapy; the survival rate at 9 years was 23% for those given prednisone monotherapy and 57% for those given prednisone in combination with azathioprine.

In summary, it seems that combined steroid and immunosuppressant therapy is usually more effective than steroid monotherapy. However, even the combined therapy achieves a response rate of only about 30%. Therefore, it remains questionable whether combined therapy is effective enough to significantly improve the prognosis of IPF.

The results of a questionnaire survey demonstrated that Japanese physicians specializing in respiratory diseases often employ symptomatic therapy when a diagnosis of IPF is made. The practical measures are used partly because assessing patients’ responsiveness to monotherapy or combined therapy requires a considerable amount of time, at least several months. In the future, it is expected that the use of serum markers for IPF, such as KL-6 and SP-D, will make it possible to evaluate the assessment of responsiveness more easily.

### Practical Alternative Treatments Available in Japan

The use of cyclophosphamide as a high-dose pulse intravenous regimen has been reported recently. This regimen consists of intravenous cyclophosphamide (10–20 mg/kg) repeated every 4 weeks. It reportedly is associated with lower incidences of adverse reactions such as hemorrhagic cystitis and malignant tumor, and at the same time allows reduced doses of steroid to be used.

It has also been reported that combination therapy with cyclosporin (Sandimmun®, Neoral®) and steroid improved both pulmonary function and dyspnea. The oral absorption of cyclosporin varies greatly among individuals. This necessitates measurement of the trough level just before dosing, and the goal should be set at about 100–150 ng/mL. Since cytochrome P-450 is largely involved in the metabolism of this agent, caution is necessary because of possible interactions with combined drugs. Tacrolimus is also being considered from the standpoints of efficacy and reduced adverse effects.

In addition to the above agents, colchicine, tranilast, neutrophil elastase, erythromycin, ACE Inhibitor, and N-acetylcycteine as an anti-oxidative stress drug have been tried either as monotherapy or in combination therapy (Table 6).
Colchicine was expected to be effective because of its inhibitory effect on the release of fibroblast growth factor from macrophages, and its efficacy in retrospective studies has been reported. However, in a study of high-dose steroid therapy and colchicine therapy, high-dose steroid was associated with serious adverse reactions, decreased lung function, and decreased survival time, while colchicine therapy was not effective.

Therapeutic attempts using interferon have been attracting attention. In a study of 18 patients with IPF unresponsive to conventional treatment, 9 patients each were randomly assigned to interferon γ-1b therapy (200 μg, 3 times a week, subcutaneously) in combination with prednisolone (7.5 mg/day) or prednisolone alone (7.5 mg/day), and followed for 12 months. The results demonstrated that the patients given interferon γ-1b showed better improvement in vital capacity and arterial oxygen tension both at rest and under loading.

The efficacy of interferon β-1a was also examined. A total of 167 patients with IPF were randomly assigned to four groups to be given placebo (43 cases) or intramuscular interferon β-1a twice weekly at a dose of 15 μg (42 cases), 30 μg (41 cases), or 60 μg (41 cases). The results indicated that interferon β-1a was not effective.

### Ongoing Therapeutic Studies

Although no collected data on treatments for IPF are available in the Cochrane Database of Systemic Reviews, the following two protocols are currently in progress. One is a study by the Cochrane Airway Group to examine the efficacy of steroid therapy, and the other is a randomized controlled study of cyclophosphamide to analyze mortality, respiratory symptoms, arterial blood gas, frequency of hospitalization, exercise tolerance, and quality of life (QOL). When the results of these studies become available, they are expected to provide firm ground for the propriety of using steroids and cyclophosphamide in the treatment of IPF.

In addition, a double-blind parallel-group placebo-controlled study of S-7701 (pirfenidone) has been carried out to determine its efficacy and safety in patients with chronic-type IPF, providing data that suggest the efficacy of this therapy.

It is well known that in cases of rheumatoid arthritis TNFα (tumor necrosis factor α) is produced from activated macrophages and is involved in inflammation. To inhibit the action of TNFα, the use of TNF receptor as a therapeutic agent has been attempted. TNF receptor is divided into two types according to molecular weight, 55 kDa and 75 kDa. Etanercept is a recombinant protein in which TNF receptor p75 is fused to the Fc portion of human IgG1. A preliminary study in 9 patients showed that it was effective in inhibiting aggravation of pulmonary function.

### From Inflammation to Epithelial Injury

The process by which chronic inflammation leads to chronic injury with subsequent fibrosis was commonly considered the core concept in the pathophysiology of IPF. However, histologic findings of cellular infiltration that can be called alveolitis are rare in surgically biopsied lung specimens from IPF patients.

Selman et al., who examined the relation...
between inflammation and fibrosis, concluded that inflammation is not indispensable to the development of fibrosis, based on the fact that there was a lack of association between the degree of inflammation and fibrosis in various animal experiments and that fibrosis can be elicited by epithelial injury alone in the absence of inflammation. This has led to the understanding that chronic inflammation is not the essential factor in determining prognosis, but that fibrosis occurs as a result of epithelial injury and defects in the subsequent healing process. Emphasis is now placed on the concept of epithelial-fibroblastic disease (Fig. 1),16,17) and therefore treatments such as those listed in Table 6 are currently being reviewed and reevaluated.

In Closing

In ending this paper, the author would like to stress the need for prudence in accepting data from Western countries as evidence for EBM. A randomized controlled study on this issue, which would be the first in Japan, is of extreme importance. However, such a study is not yet feasible under current circumstances in Japan. In order to promote patients’ understanding of such studies, efforts aimed at the disclosure of pertinent information would be desirable.

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