

Steroids and/or cytotoxic agents should be used early in the management of patients with IPF – The pro argument

Sat Sharma MD FRCPC

Idiopathic interstitial pneumonias comprise a heterogeneous group of acute and chronic respiratory conditions. Katzenstein and Myers (1) classified these disorders according to several pathologically distinct categories: usual interstitial pneumonitis (UIP), desquamative interstitial pneumonitis – respiratory bronchiolitis interstitial lung disease, acute interstitial pneumonitis, nonspecific interstitial pneumonitis and cryptogenic organizing pneumonitis or bronchiolitis obliterans organizing pneumonia (1). These disorders present with similar clinical features of shortness of breath, diffuse pulmonary infiltrates on chest radiograph, and histologically, a varying combination of inflammation and fibrosis. However, the natural history and response to therapy differs substantially, as some categories have more favourable prognoses than others (2). Idiopathic pulmonary fibrosis (IPF) or fibrosing alveolitis is the clinical terminology for a specific interstitial pneumonia for which the pathological process is UIP. A disorder of unknown etiology, IPF is the most common and most lethal of all interstitial pneumonias.

PROGNOSIS OF IPF

IPF is a more common disease than previously thought; the incidence is estimated to be 10.7 cases/100,000 men and 7.4 cases/100,000 women (3). A population-based study reported the prevalence to be 20.2 and 13.2 cases/100,000 men and women, respectively (3). The diagnosis of IPF carries a grave prognosis. From the time of diagnosis, the mean length of survival is documented to be between 3.2 and five years (2,4). A recent cohort study found a median length of survival of 2.9 years for incident cases and nine years for prevalent cases (5).

Although IPF is an inexorably progressive disease, three separate phases have been identified (6). An initial stable phase consists of stable lung functions and no or minimal symptoms. During the symptomatic phase, the patient becomes increasingly dyspneic and desaturates on exercise, and lung functions worsen to a level of between 50% and 80%. The final stage of rapid decline is characterized by dyspnea and hypoxemia at rest, lowering of vital capacity to less than 50%, respiratory failure and progression to death.

PATHOGENESIS OF IPF

Pathogenesis of IPF appears to be instigated by four different cells, as well as numerous proteins and mediators. The neutrophils and alveolar macrophages secrete various cytokines, including interleukin-8, tumor necrosis factor-alpha and oxygen free radicals (7). The T lymphocyte, a major immunoregulatory cell, plays an important role in the initiation and perpetuation of pulmonary fibrosis (8). A Th-1 immune response is mediated by the cytokine interferon-gamma; this mediator is generally prevalent in high levels in granulomatous disorders such as sarcoidosis. The inflammatory response in IPF has been associated with an unregulated Th-2 immune response. The Th-2 cytokines interleukin-4 and interleukin-13 modulate tissue injury and lead to the development and progression of pulmonary fibrosis (9). Finally, fibroblast activation via cytokine interleukin-8 and others, accompanied by expression of transforming growth factor-beta and connective tissue growth factor, promotes the deposition of extracellular matrix, collagen deposition and fibrosis (10).

TREATMENT OF IPF

IPF characteristically has a progressive clinical course and a poor prognosis; therefore, it is prudent to consider an early and aggressive approach to therapy. Because IPF is an immune-mediated disease, and inflammation leads to injury and fibrosis, anti-inflammatory and immunosuppressive therapy is logical. Recent research has focused on modifying the fibroblast activity with antifibrotic agents, including colchicine, pirfenidone, relaxin and endothelin-1 blockers (11,12). Immunomodulators such as interferon-gamma, a Th-1 cytokine, inhibit transforming growth factor-beta₁ and, thus, Th-2-induced inflammatory processes (13,14). The antifibrotic and immunomodulator therapies are under investigation and are not presently approved for clinical use. The data for currently available therapy suffer from several limitations: heterogeneous patients, disparate study designs, lack of placebo controls, variable doses and durations of treatment, and inadequate outcome assessments. Despite these limitations, the only contemporary rational treatment option for treating this devastating disease process remains corticosteroids (CSs) and/or cytotoxic agents. However, the anti-inflammatory

Sections of Respiriology and Critical Care Medicine, University of Manitoba, Winnipeg, Manitoba

Correspondence and reprints: Dr Sat Sharma, BG 034, St Boniface Hospital, 409 Tache Avenue, Winnipeg, Manitoba R2H 2A6.

Telephone 204-237-2217, fax 204-231-1927, e-mail ssharma@mb.sympatico.ca

therapy needs to be instituted early. Unfortunately, a clinical nihilism prevails in the medical community pertaining to the pharmacological treatment of IPF. Therefore, most patients already have advanced disease at the time of referral to pulmonary specialists. Most experts advocate early diagnosis and aggressive treatment for appropriate patients with interstitial lung disease secondary to IPF.

CORTICOSTEROIDS

Despite being the mainstay of therapy for the past several decades, no prospective, randomized, placebo-controlled trial has demonstrated the efficacy of CSs in IPF. Several studies have documented response rates of 10% to 30% as defined by quantitative criteria (15-18). Based on subjective assessment, up to 40% of CS-treated patients acknowledged improvement.

A prospective, nonrandomized study of high dose CS therapy by Flaherty et al (19) showed a higher survival rate in steroid responders. In that study, 27% of patients with IPF improved, 46% remained stable and 27% deteriorated. However, recent retrospective data from the Mayo Clinic demonstrated a lack of benefit from CS therapy (20). Randomized trials comparing CSs with cytotoxic agents or colchicine in patients with IPF have been published. Although initial improvement occurred in patients taking CSs, long term outcomes were unfavourable. Lack of CS efficacy from these trials is difficult to assess because treatment was generally prescribed to the patients with advanced or irreversible stages of IPF. Because of the potential for many serious side effects and limited long term benefit, most experts discourage the use of CSs alone in these patients (21).

CYTOTOXIC AGENTS – AZATHIOPRINE OR CYCLOPHOSPHAMIDE

Previously, these agents were used in steroid nonresponders, to reduce steroid side effects, and in patients at high risk for morbidity from CSs. Over the past several decades, several clinical trials were conducted in IPF patients with CSs alone or CSs plus azathioprine (AZA) or cyclophosphamide (CP). A favourable response was obtained in 15% to 50% of patients treated with immunosuppressives, because multiple mechanisms possibly enhance their therapeutic efficacy.

Winterbauer et al (22) demonstrated an improvement in lung function in IPF patients treated with CSs and AZA compared with CSs alone. A randomized, placebo-controlled trial by Raghu et al (23) showed improved lung function in CS- and AZA-treated patients at one-year intervals. After nine years of follow-up, a survival advantage (mortality rate 43% versus 77%) was seen in CS plus AZA-treated patients (23).

CP has been shown to benefit patients with pulmonary fibrosis secondary to scleroderma. A cohort study of 103 patients showed preservation of lung function and higher survival rates (81% versus 71%) with CP (24). Likewise, several published studies have established the benefits of CP therapy in patients with IPF. Johnson et al (25) demonstrated improved lung function in seven of 21 patients treated with CP and CSs compared with two of 22 patients treated with CSs alone. An overall survival advantage was evident in CP plus CS-treated

patients. In another study by Baughman et al (26), intravenous CP was associated with improved pulmonary function and a reduction in steroid dose. Dayton et al (27) reported improvement in one and stabilization in seven of 19 patients with IPF taking oral CP. Similarly, Kolb et al (28) showed stabilization of lung function with CP pulse therapy, whereas Zisman et al (29) found limited efficacy with oral CP. More recently, cyclosporine A improved the clinical status of patients with various interstitial pneumonias, including UIP (30).

RECOMMENDATIONS FROM THE AMERICAN THORACIC SOCIETY AND THE EUROPEAN RESPIRATORY SOCIETY (INTERNATIONAL CONSENSUS STATEMENT, JULY 1999)

After discussing the risks and benefits of therapy, the following treatment may be offered to patients with IPF: CSs (0.5 mg/kg initially, tapered over eight weeks to 0.125 mg/kg) plus AZA at 2 mg/kg to 3 mg/kg (starting at 25 mg to 50 mg and then gradually increasing) or CP at 2 mg/kg (beginning at 25 mg to 50 mg and increasing gradually) (21).

CONCLUSIONS

IPF is a relentlessly progressive disorder with a bleak prognosis. Early aggressive therapy offers the only chance of affecting the staggering mortality in individuals afflicted with IPF. In the future, newer drugs, especially interferon-gamma, relaxin, bosentan and pirfenidone, may prove to be quite beneficial. Lung transplantation may be an option for younger patients.

However, CSs and cytotoxic agents remain the standard therapy for patients with IPF. The international consensus statement echoes this sentiment:

"The exact time that therapy should be started is unknown. The committee believes that response rates may be higher when treatment is initiated early in the course of the disease, before irreversible fibrosis has developed. Failure in some cases appears to reflect delays in initiating treatment. Therefore, the committee recommends that if therapy will be offered to a patient, it should be started at the first indication of clinical or physiological evidence of impairment or documentation of decline in lung function" (21).

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