EDITORIAL

New Treatments for Idiopathic Pulmonary Fibrosis

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Idiopathic pulmonary fibrosis is the most common type of idiopathic interstitial pneumonia and the type with the least favorable prognosis. The median survival of patients with idiopathic pulmonary fibrosis is from 2 to 3 years with the new classification,[1-3] in other words, less than the 5-year median reported in previous studies that included other idiopathic pneumonias with better prognoses.

The most important advance in the last 10 years has been a new histologic classification[1] that has deepened our understanding of the natural history of idiopathic pulmonary fibrosis, its prognosis, and many of the biological changes it brings about. Unfortunately, such progress has not been accompanied by commensurate advances in treatment; the only achievement has been confirmation that current treatment techniques improve neither survival rates nor the quality of life of patients with idiopathic pulmonary fibrosis. However, concepts that have emerged from the new classification may be of great use in investigating new treatments.[4] Knowing that fibrosis is the most important prognostic factor enables researchers to focus their investigation on antifibrotic drugs, thereby opening up a new era in the treatment of the disease. For decades the main hypothesis regarding the pathogenesis of idiopathic pulmonary fibrosis was that the initial event was an inflammatory process that led to alveolitis with fibroblast–myofibroblast formation, collagen deposition, and irreversible fibrosis. This inflammatory hypothesis has justified treatment with corticosteroids and immunodepressants and, although most current research groups question the hypothesis, others believe there is still reason to consider an inflammatory mechanism in idiopathic pulmonary fibrosis. Thus, from the study of multiple biopsies, Flaherty et al[5] and Monogham et al[6] obtained the following results: the findings of nonspecific interstitial pneumonia (NSIP) and usual interstitial pneumonia (UIP) were discordant in 26% of the patients, the prognoses of the 26% were similar to that of the group in which only UIP findings were observed, and the patients with NSIP were younger. Such findings led the authors to consider a possible progression of NSIP to UIP and, consequently, a possible role of chronic inflammation in the initial stages of the disease. However, detractors of the inflammatory hypothesis reject the progression hypothesis for various reasons: the most characteristic feature of idiopathic pulmonary fibrosis is the formation of fibroblastic foci; studies carried out on animals have failed to demonstrate a relation between the inflammation and the fibrosis; inflammatory markers are unrelated to prognosis in this disease; and, perhaps the most convincing reason, treatment with anti-inflammatory drugs has not been shown to alter outcome. Another finding that weighs in against the theory that NSIP could be the initial phase or an inactive form of UIP recently came from Katzestein and colleagues,[7] who compared explanted lungs with biopsies taken prior to transplantation: they observed areas of NSIP in the explanted lung that were not present in the biopsies. It is difficult to interpret findings from such a small number of cases, but perhaps larger studies based on more clinical and radiological data could help explain many of the discrepancies that are observed between clinical manifestations and histologic evaluation. Important issues in evaluating treatment based only on histological information are the histological variability of idiopathic pulmonary fibrosis and the problem of whether or not the samples taken are representative of the lung. Therefore clinical and cardiological criteria for treatment should take precedence in case of disagreement. However, the underlying concept that idiopathic pulmonary fibrosis is primarily an epithelial–fibroblastic disease in which inflammation is secondary explains the failure of anti-inflammatory treatment and justifies the testing of new drugs that truly target fibrosis.

The latest research on the pathogenesis of pulmonary fibrosis indicates that there is excessive deposition of extracellular matrix, failure of the normal remodeling mechanism, and abnormal angiogenesis. Use of broad-spectrum antifibrotic drugs,[8] such as colchicine and D-penicillamine, has not improved survival rates. Consequently, a search for more selective antifibrotic agents seems appropriate. Such agents should have the capacity to both inhibit proliferation and increase apoptosis of fibroblasts and myofibroblasts, decrease the synthesis and deposition of extracellular matrix, and promote restoration of normal architecture. Since the ideal antifibrotic agent has not yet been found, one option for treating this complex disease consists of using various drugs with different mechanisms of action.

Interferon-γ,[9-12] pirfenidone,[13] antioxidants (N-acetyl-cysteine), anti–tumor necrosis factor-α antibodies, and endothelin receptor antagonists are the pharmaceuticals in the most advanced phases of study and those with which we have the most experience.

Interferon-γ is the most commonly used antifibrotic drug. The first trial by Ziesche et al[9] with 18 patients obtained better survival in the group treated with prednisone and interferon than in the group treated only

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with prednisone. Later it was observed that some of the cases did not strictly meet the definition of UIP. In a subsequent study Prasse et al[10] obtained less optimistic results than those of Ziesche and colleagues. Since both those trials enrolled small samples, another study was carried out with 330 patients.[11] The results showed no statistically significant differences in survival rates overall but did show significantly lower mortality in the patients with more than 55% vital capacity when the study started. These findings indicate that treatment with prednisone and interferon may be effective in the initial phases of the disease. Accordingly, an even larger trial is presently being carried out with the aim of either confirming or rejecting the hypothesis. Pirfenidone, another antifibrotic agent, has been used with promising initial results; definitive results of several phase III trials are still pending. N-acetylcysteine and anti–tumor necrosis factor-α antibodies are other pharmaceuticals that have been used in recent trials, the definitive results of which are yet to be reported. Several new drugs —such as antigrowth factor antibodies, analogs of thalidomide, mycophenolate, rapamycin, suramin, relaxin, and so on—can also be considered antifibrotic agents and will probably be analyzed in future studies.

There is reason for optimism. Pharmaceuticals developed based on what we know of the initial causes of idiopathic pulmonary fibrosis are being tested. However, given the complexity of the inflammatory and fibrotic mechanisms of the disease, we are probably only at the start of a long, hard road as Silverman and Talbot[14] predicted 50 years ago when they commented that the rarity of interstitial pulmonary fibrosis, the difficulty in establishing an early diagnosis, and our ignorance of its etiology would present nearly insurmountable obstacles to managing this complex disease.

From the failure of medical treatment emerges lung transplantation, which is the therapeutic option of last resort—one that is only a possibility for a minority of patients. Even those who make the waiting lists have high mortality rates before the procedure and during the first post-transplant year.[15,16] High waiting list mortality and the lack of organs for candidates reflect our poor understanding of the evolution of the disease and the difficulty in determining optimum time for transplantation. A recent study provided a model to help optimize time of referral for transplantation based on percentage of carbon monoxide diffusing capacity and degree of fibrosis as observed by high resolution computerized tomography.[17] Also in an effort to reduce high mortality rates, wait-listed patients with idiopathic pulmonary fibrosis are given a certain priority by some transplant organizations, such as the Network for Organ Sharing and the Euro Transplant group. With these measures lung transplantation has become, at present, the only treatment that improves the quality of life and survival of patients with idiopathic pulmonary fibrosis despite markedly high mortality rates during the first year—surpassed only by the mortality rate of patients transplanted for pulmonary hypertension.[18] It is not known whether the high mortality rate of idiopathic pulmonary fibrosis patients is due to the disease itself or to other factors such as age and the presence of comorbidity.

In summary, experience so far is characterized by a lack of effective medical or surgical treatments for idiopathic pulmonary fibrosis. Advances in histological classification and in our understanding of initial causes, as well as the possibility of studying explanted lungs, have given rise to new drug lines and stimulated research into the complex histology of this disease. If we could identify patients who do not respond to corticosteroids, iatrogenic adverse events could be avoided and other therapeutic options with fewer side effects could be prescribed. Avoiding side effects of ineffective treatment is a fundamental principle in medicine and is especially crucial for patients who are candidates for lung transplantation.

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