EDITORIAL

Localizador web
Artículo 144.925

Serum Markers in Idiopathic Pulmonary Fibrosis. Implications for Prognosis

Orlando Acosta Fernández

Servicio de Neumología, Hospital Universitario Nuestra Señora de la Candelaria, Santa Cruz de Tenerife, Spain.

Published recommendations on the diagnosis and treatment of idiopathic pulmonary fibrosis (IPF) are aimed at conceptualizing the development of the disease and assessing response to treatment.[1,2] The 3 IPF categories defined—improvement, stabilization, and deterioration—are based on the magnitude of percentage variations in forced vital capacity or carbon monoxide diffusing capacity, absolute variations in the alveolar-arterial oxygen pressure difference, and clinical and radiological course over time (specifically the degree of dyspnea). When attempting to establish whether a patient is improving, deteriorating, or stabilizing on the basis of functional tests, it is frequently difficult to assess in absolute terms the clinical significance of any minor variations in the above-mentioned parameters. This difficulty is further aggravated if the observed trends in recorded values do not concur with the patient's own subjective evaluation of their disease or if the patterns analyzed do not behave in a coherent way. Likewise, the subjectivity of radiologists and their experience in evaluating chest diseases may affect any assessment as to radiological improvement or deterioration, most particularly if alterations such as ground-glass opacity or honeycombing are not systematically quantified and recorded in the form of scores.[3]

Although it is widely acknowledged that the most important factor in determining prognosis and survival for patients with idiopathic interstitial pneumonias is the histological pattern of the disease in the lung,[4] the percentage of patients who actually undergo a lung biopsy does not usually exceed 30%. Irrespective of whether histological or clinical and radiological criteria are used to arrive at a diagnosis, patients are generally monitored on the basis of a combined analysis of the clinical, radiological, and functional variables referred to above. Nonetheless, our understanding of the pathogenic mechanisms of IPF has improved in recent decades,[5,6] and this has led to a persistent search for serum markers that would enable a possible therapeutic response in a patient to be estimated, serve as useful activity markers for patient monitoring, and finally, predict patient survival. We will now review some of the markers that have proven useful in monitoring IPF and assessing prognosis.

The KL-6 antigen is a high molecular weight glycoprotein produced by damaged type 2 pneumocytes or pneumocytes in the process of regeneration. High levels of KL-6 are found in the bronchoalveolar lavage of a large percentage of patients with IPF[7] or with pulmonary fibrosis secondary to schlerodermia.[8] High KL-6 concentrations are not specific to IPF, however, as levels may also be elevated in carriers of certain malignant neoplasms; moreover, it has not been conclusively demonstrated that circulating KL-6 levels predict the course of IPF. Nonetheless, in the absence of neoplastic disease, higher concentrations of this serum marker may well be associated with a worse clinical course. Of note are the findings of Yokohama et al,[9] who observed a tendency for circulating KL-6 values to fall within the week after administration of corticosteroid pulse therapy to patients experiencing an IPF exacerbation. The authors pointed to this response as a predictor of the course of disease, in that an early reduction in these values would indicate a favorable clinical response.

The metalloproteinases (MMPs) are protein molecules produced by alveolar epithelial cells, macrophages, and neutrophils. It is now known that they play an important role in fibrosing initiation and progression through their interactions with a range of cytokines, such as the insulin-like growth factor, transforming growth factor (TGF) β, and tumor necrosis factor α. The MMPs regulate protein exchange in the extracellular matrix; their enzymatic activity, on the other hand, is controlled by tissue inhibitors of metalloproteinases (TIMPs). The imbalance in the MMP/TIMP ratio that can be observed in the lungs of patients with IPF may partially explain anomalous fibrotic remodeling in the lung.[10,11] These markers, therefore, should be analyzed in the serum of patients with IPF.

Correspondence: Dr. O. Acosta Fernández.
Servicio de Neumología. Hospital Universitario Nuestra Señora de la Candelaria.
Ctra. del Rosario, s/n. 38010 Santa Cruz de Tenerife. España.
E-mail: oacosta@comtf.es

Manuscript received January 10, 2006. Accepted for publication January 31, 2006.

The monocyte chemotactic protein-1 (MCP-1) is produced by macrophages, alveolar epithelial cells, and endothelial cells. Suga et al[12] demonstrated that the bronchoalveolar lavage and serum ratios for MCP-1 in IPF cases were significantly higher than for other illnesses, such as pulmonary disease associated with collagen disease, nonspecific interstitial pneumonias, and sarcoidosis. The measurement of MCP-1 levels in bronchoalveolar lavage fluid and serum is, therefore, potentially useful. More interesting, perhaps, is the observation by the same authors, that despite treatment with corticosteroids, MCP-1 levels increased in IFP patients with a poor prognosis, but fell in patients who were evolving favorably.

The surfactant A and D proteins (SP-A and SP-D) are hydrophilic proteins with low molecular weights. They belong to the C-type lectin superfamily and are produced by type 2 pneumocytes and clear cells. Several studies have associated alveolar surfactant components with—among other functions—regulation of extracellular matrix protein synthesis, degradation, and deposition, and also with fibroblastic proliferation and activity. Takahashi et al[13] found that high serum values for SP-D predicted a rapid deterioration in lung function and also that high serum values for SP-A and/or SP-D were indicators of lower survival. Other authors have corroborated this link between high serum concentrations for these markers and survival rates.[14,15]

Of the known cytokeratins, high levels of fragment 19 (CYFRA)—which had originally been evaluated as a biomarker for bronchogenic cancer—have been found in patients with IPF or with interstitial disease associated with collagen disease; this fact is possibly related to the destruction of the alveolar epithelium or repair of a damaged alveolar epithelium. In their study, Nakayama et al[16] reported high serum values for this protein in 50% of patients with IPF; more significantly, they observed that higher serum levels predicted a lower survival rate.

A cytokine playing a very important role in initiating and terminating tissue repair is TGF-β_1, whose overexpression in the lung can lead to fibrosis, as demonstrated in animal models.[17] TGF-β_1 is basically synthesized by alveolar macrophages. Activated when a tissue lesion occurs, it facilitates chemotactic activity leading to an inflow of neutrophils, T lymphocytes, monocytes, and fibroblasts.[5,18] Thus, complex pathophysiologic phenomena in the tissues ultimately lead to the synthesis and deposition of extracellular matrix proteins (fibronectin, proteoglycans, and type 1 collagen), a reduction in protease activity, an increase in antiprotease synthesis, and a reduction in myofibroblast apoptosis. They also facilitate fibroblastic differentiation and lead to increased integrin activity; these, in turn, favor cell adhesion to the matrix. In cases of limited lung injury, the increase in TGF-β_1 is transitory and fibrosis is minimal or non-existent. If fibrosis is recurrent, however, increased TGF-β_1 production is sustained, and this in turn facilitates fibrosis. It is quite probable that autoinduction of TGF-β_1 synthesis is involved in lung fibrosis, as this would explain the progression of pulmonary disease even when the lesion mechanism is no longer active.

Significantly higher levels of TGF-β_1 were observed in IPF patients in a case-control study by Suk-Joong et al.[19] Furthermore, in a small number of cases corticosteroid treatment led to a clear reduction in serum levels of this biomarker, although the levels continued to be higher than for patients in the control group.

In this issue of ARCHIVOS DE BRONCONEUMOLOGÍA Molina-Molina and colleagues[20] report an interesting study in which they take a novel approach. Their main aim was to consider the prognostic value of serum TGF-β_1 levels in a sample of 13 patients with IPF monitored over a period of 8 months. Like Suk-Joong et al,[19] they observed higher TGF-β_1 levels in patients compared to controls, but found no association with disease activity following a series of measurements of this parameter. Nonetheless, certain considerations should be mentioned. The article describes variations in the functional parameters that were monitored in the patients; even without information on the evolution of the alveolar-arterial oxygen pressure difference, it can be stated that the changes were minimal, give that mean deterioration was approximately 3% to 4% in forced vital capacity and 10% to 12% in carbon monoxide diffusing capacity. Given these variations, the overall view is that the monitored patients remained functionally stable. It would be relevant, therefore, to analyze how measured serum levels of TGF-β_1 would change if there was significant functional deterioration or improvement, or if there were clear clinical, radiological, and functional changes. The authors pointed to high TGF-β_1 serum levels in patients (compared to controls) as characterizing the existence of a pulmonary fibrosing disease. However, they should not rule out a prognostic value for this marker; taking a general view, the changes in the lung function of the monitored IPF patients were not of sufficient magnitude. Of benefit would be a longer study of a larger patient cohort. Future studies should also analyze both serum behavior of TGF-β_1 in exacerbations and predictions as to survival.

In conclusion, a number of serum markers—for which both sensitivity and specificity have been demonstrated—have proven to be of use in characterizing the fibrosing process in IPF. Some of these markers have been revealed to be closely tied to the course of disease and therapeutic response to corticosteroids; some have even been proven to be acceptable predictors of mortality. Nonetheless, clinical use of these markers is not widespread. One possible reason is the difficulty implied by implementing large-scale cohort studies of patients with IPF, who should ideally have a histological diagnosis, who should present with coherent clinical, radiological, and functional characteristics, and for whom long-term monitoring should be possible. The study by Molina-Molina et al[20] should encourage those interested in understanding this complex disease to continue and/or implement the kind of ambitious study that is so much needed.

REFERENCES

1. Idiopathic pulmonary fibrosis. International Consensus Statement. Am J Respir Crit Care Med. 2000;161:646-64.
2. Xaubet A, Ancoechea J, Blanquer R, Montero C, Morell F, Rodríguez-Becerra F, et al. Diagnóstico y tratamiento de las enfermedades intersticiales difusas. Arch Bronconeumol. 2003;39:580-600.
3. Lynch D, Travis W, Müller N, Galvin J, Hansell D, Grenier P, et al. Idiopathic interstitial pneumonias: CT features. Radiology. 2005;236:10-21.
4. Flaherty K, Toews G, Travis W, Colby T, Kazerooni E, Gross B, et al. Clinical significance of histological classification of idiopathic interstitial pneumonia. Eur Respir J. 2002;19:275-83.
5. Noble P, Homer R. Idiopathic pulmonary fibrosis: new insights into pathogenesis. Clin Chest Med. 2004;25:749-58.
6. Antoniou KM, Alexandrakis MG, Siafakas NM, Bouros D. Cytokine network in the pathogenesis of idiopathic pulmonary fibrosis. Sarcoidosis Vasc Diffuse Lung Dis. 2005;22:91-104.
7. Kohno N, Awaya Y, Oyama T, Yamakido M, Akiyama M, Inoue Y, et al. KL-6, a mucin-like glycoprotein, in bronchoalveolar lavage fluid from patients with interstitial lung disease. Am Rev Respir Dis. 1993;148:637-42.
8. Yamane K, Ihn H, Kubo M, Yasawa N, Kikuchi K, Soma Y, et al. Serum levels of KL-6 as a useful marker evaluating pulmonary fibrosis in patients with systemic sclerosis. J Rheumatol. 2000;27:930-4.
9. Yokohama A, Khono N, Hamada H, Sakatani M, Ueda E, Kondo K, et al. Circulating KL-6 predicts the outcome of rapidly progressive idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 1998;158:1680-4.
10. Selman M, Ruiz V, Cabrera S, Segura L, Ramírez R, Barrios R, et al. TIMP-1,-2,-3 and –4 in idiopathic pulmonary fibrosis. A prevailing nondegradative lung microenvironment? Am J Physiol Lung Cell Mol Physiol. 2000;279:562-74.
11. Winkler M, Fowlkes J. Metalloproteinase and growth factor interactions; do they play a role in pulmonary fibrosis? Am J Physiol Lung Cell Mol Physiol. 2002;283:1-11.
12. Suga M, Yyonaga K, Ichiasu H, Saita N, Yamasaki H, Ando M. Clinical significance of MCP-1 levels in BALF and serum in patients with interstitial lung diseases. Eur Respir J. 1999;14:376-82.
13. Takahashi H, Fujishima T, Koba H, Murakami S, Kurokawa K, Shibuya Y, et al. Serum surfactant proteins A and D as prognostic factors in idiopathic pulmonary fibrosis and their relationship to disease extent. Am J Respir Crit Care Med. 2000;162:1109-14.
14. Greene K, King TE Jr, Kuroki Y, Bucher-Bartelson B, Hunninghake GW, Newman LS, et al. Serum surfactant proteins-A and -D as biomarkers in idiopathic pulmonary fibrosis. Eur Respir J. 2002;19:439-46.
15. Ohnishi H, Yokohama A, Kondo K, Hamada H, Abe M, Nishimura K, et al. Comparative study of KL-6, SP-A, SP-D and MCP-1 as serum markers for interstitial lung diseases. Am J Respir Crit Care Med. 2002;165:378-81.
16. Nakayama M, Sayoh H, Ishikawa H, Fujiwara M, Kamma H, Ohtsuka M, et al. Cytokeratin 19 fragment in patients with nonmalignant respiratory diseases. Chest. 2003;123:2001-6.
17. Sime, PJ, Marr, RA, Gauldie, D, et al. Transfer of TNF-alpha to rat lung induces severe pulmonary inflammation and patchy interstitial fibrogenesis with induction of transforming growth factor-beta1 and myofibroblasts. Am J Pathol 1998;153,825-32
18. Border W, Noble N. Transforming growth factor β in tissue fibrosis. N Engl J Med. 1994;331:1286-94.
19. Suk-Joong Y, Adlakha AH, Limper A. Circulating transforming factor β. A potential marker of the disease activity during idiopathic pulmonary fibrosis. Chest. 2001;120:68S-70S.
20. Molina-Molina M, Lario S, Luburich P, Ramírez J, Carrión MT, Xaubet A. Determinación en plasma del factor transformador del crecimiento β_1 en la fibrosis pulmonar idiopática. Arch Bronconeumol. 2006;42:380-3.