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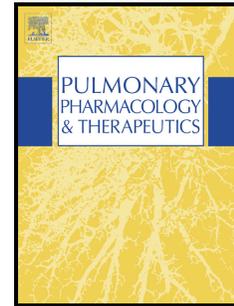
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Title: Serum biomarkers in idiopathic pulmonary fibrosis

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Abstract

Within the group of Idiopathic Interstitial Pneumonias (IIPs), above all Idiopathic Pulmonary Fibrosis (IPF) poses a considerable diagnostic and therapeutic problem. Although genetic profiling indicates that IPF, Non Specific Interstitial Pneumonia (NSIP), and chronic hypersensitivity pneumonitis (HP) are distinctly different diseases, in every day practice these diseases can be difficult to tell apart. Furthermore, treatment of these diseases is notoriously difficult. Serum biomarkers reflect our understanding of the underlying pathogenesis and potentially fulfill a role in establishing a diagnosis, prognosis and therapy. While no single biomarker is currently able to accurately predict the presence or absence of an IIP, a composite of several markers holds promise for the future. Several biomarkers, such as KL-6, surfactant proteins and circulating fibrocytes, appear to contribute to our insight into disease progression and prognosis. It is however uncertain whether these markers give us additional information to common diagnostic tests and their value has as yet to be validated for every day practice. Fortunately, the potential of biomarkers is increasingly recognized and biomarker data are prospectively gathered in current placebo-controlled therapeutic trials.

1 Introduction

Diffuse parenchymal lung disease, synonymous with the more current name interstitial lung disease (ILD) comprises a heterogeneous group of lung diseases affecting the interstitium, the space between epithelial and endothelial basement membrane, but often also the alveolar epithelium, small airways and vessels. The cause of ILDs varies widely, including medication effects, toxic inhalation, in association with connective tissue disease (CTD), or may be idiopathic.

With the advent of the ATS/ERS classification of ILDs, a powerful tool was generated for distinguishing more precisely defined patient groups, facilitating international discussions and collaborations on ILD research, resulting in an unprecedented number of clinical trials [1]. Despite these efforts current therapy is often ineffective. Among the Idiopathic Interstitial Pneumonias (IIPs), especially idiopathic pulmonary fibrosis (IPF) and nonspecific interstitial pneumonia (NSIP) often pose considerable diagnostic and therapeutic dilemmas.

IPF, the most common IIP, is a devastating fibrosing lung disease of unknown cause. The majority of IPF patients are older than 60 years at the time of diagnosis, often current or former smokers, with gradual onset of dyspnea with a non-productive cough. On physical examination, bibasilar fine inspiratory crackles are typically heard and digital clubbing is seen in 25 to 50% of patients. There are usually no signs of auto-immune disease. Pulmonary function tests reveal a restricted lung-volume with impaired gas exchange. High-resolution computed tomography (HR-CT) may show bilateral subpleural reticular changes with a basal predominance with traction bronchiectasis and honeycombing. A typical clinical presentation combined with characteristic HR-CT abnormalities can lead to a confident clinical diagnosis of IPF in a multidisciplinary setting, obviating the need for surgical lung biopsy. When clinical and/or HR-CT features are not considered typical of IPF, a surgical lung biopsy is often obtained. On surgical lung biopsy, IPF is associated with a histopathologic pattern of a Usual Interstitial Pneumonia (UIP). The disease's natural course invariably leads to a fatal outcome and with a mean prognosis of approximately 3 years it is not only the most common, but also by far the most deadly of all IIPs. [1-2]. Evidence-based therapy for IPF is lacking. For example, the 2008 BTS statement on ILDs only weakly recommends one therapy for IPF [3].

Distinguishing IPF from idiopathic NSIP, using the 2002 ATS/ERS classification of ILDs, can be difficult and there has been an ongoing debate whether idiopathic NSIP is a separate entity. Currently, idiopathic NSIP is thought to form a distinct IIP [4]. Idiopathic NSIP occurs mostly in middle-aged women who never smoked, presenting with dyspnea and cough. There is usually no clubbing, auto-immune serology for antinuclear antibodies or rheumatoid factor may be positive and pulmonary function tests often reveal a restricted lung-volume. Typically, on HR-CT a reticular pattern with traction bronchiectasis is observed in the lower lung zones in a peripheral or diffuse distribution. Ground-glass attenuation is a common feature, in contrast to IPF. On surgical lung biopsy, histopathologic features range from a cellular pattern with mild interstitial chronic inflammation to a fibrotic pattern with interstitial fibrosis with a uniform appearance. In order to confidently diagnose an idiopathic NSIP, a multidisciplinary

setting is advised to reach a consensus clinical-radiologic-pathologic diagnosis. In contrast to IPF, the majority of patients with idiopathic NSIP have a good prognosis [4]. A histopathologic NSIP pattern is also associated with a variety of conditions such as drug reactions, organic dust exposure and CTD. Indeed, a NSIP pattern is the most common histopathologic pattern in CTD-associated interstitial pneumonias and may even precede an overt clinical CTD. Interestingly, a large proportion of patients with idiopathic NSIP was reported to exhibit signs of undifferentiated connective tissue disease [5].

2 Diagnostic and therapeutic dilemma's in IPF

Several problems face the clinician in diagnosing and treating patients with IPF: establishing the proper diagnosis, estimating a prognosis, choosing and evaluating therapy. There is no 'gold standard' for the diagnosis of IPF. A fairly confident diagnosis can be made in a large proportion of patients based on clinical and radiographic data, according to the ATS/ERS statement criteria [1]. In some instances a clear diagnosis is not easily made. Atypical radiographic or clinical presentation combined with an impossibility to obtain an open lung biopsy may make differentiation from chronic hypersensitivity pneumonitis (HP) or fibrotic NSIP difficult. Even with an open lung biopsy, a confident diagnosis is not always made, for example due to a sample showing mere 'end-stage lung' or discrepancies between clinical presentation, radiology and histology. Preferably, a consensus diagnosis is then made between clinician, radiologist and pathologist. A diagnosis reached in this multidisciplinary setting currently often serves as the 'gold standard' [3]. However, the clinical setting of this diagnostic process influences the outcome significantly, and even between experienced radiologists and pathologists there is considerable inter-observer variation, invariably implying a diagnostic uncertainty [6-7]. Thus, the diagnosis of IPF is often one with a, variable, diagnostic uncertainty.

Several types of disease progression have been described for IPF. Next to patients that deteriorate slowly, patients can suffer from rapidly progressive fibrosis or sudden deterioration due to acute exacerbations, both associated with a poor prognosis. Identification of these patients could possibly single out patients most likely to benefit from medical therapy, clinical trial or early lung transplantation listing. Furthermore, identification of patients with an indolent disease course could prevent unnecessary therapy and concomitant side-effects. In daily practice, identifying patients at risk for accelerated fibrosis or acute exacerbations, both associated with high mortality, is notoriously difficult [2, 8-9].

To date, no medical therapy has convincingly proven to alter the natural course of the disease, with the possible exception of pirfenidone in Japanese patients [10]. Patients and caregivers are thus in desperate need for better markers for disease identification, identifying patients at risk for disease progression and identifying those who will benefit from therapy. Biomarkers could potentially fulfill this role. Gene profiling studies on lung biopsy material indicate distinct gene expression patterns in patients with stable and progressive IPF and in patients with an exacerbation of IPF. Furthermore, gene expression patterns in IPF were found to be different from HP and in a proportion of cases from NSIP.

These data support the notion that (patterns of) biomarkers could serve as a diagnostic and prognostic tool in IPF [11-13].

3 Serum biomarkers in IPF

3.1 Candidate biomarkers

Biomarkers investigated in idiopathic fibrosing lung diseases reflect and perhaps broaden our current understanding of the events underlying the scarring of the lung. Research into the pathogenesis of IPF has advanced considerably in recent years and has shifted its focus from processes governing chronic inflammation with fibrosis as end result, to alveolar epithelial dysfunction and injury with aberrant wound repair and disordered fibroproliferation [14-15]. A range of molecules involved in epithelial damage and repair (eg surfactant-protein (SP)-A, and SP-D, Krebs von den Lungen (KL)-6, Clara cell secretory protein (CC)-16), inflammation (CD28, MCP-1, MIP1a, CXCL-11, TNF, LDH, sIL-2R, CCL-18), myofibroblast accumulation and matrix deposition (circulating fibrocytes, Heat shock protein 47 (HSP47), matrix metalloproteinases (MMPs), TGF β), angiogenesis (vascular endothelial growth factor (VEGF), IL-8), coagulation and oxidative stress [16], have been described as potential serum, BAL and tissue biomarkers [17-20]. Biomarkers should ideally be easily obtained in a non-invasive manner and validated for use in every day practice. Serum biomarkers have the advantage that they can be measured non-invasively and are easily suitable for follow-up. Several of these biomarkers seem promising and will be discussed here in more detail.

3.2 KL-6

KL-6 is a high molecular weight, mucin-like glycoprotein, expressed on the surface of various epithelial cells. KL-6 was found to be highly expressed by regenerating type II pneumocytes in tissue sections from patients with interstitial lung diseases [21]. Upon epithelial breakdown, KL-6 is thought to leak into the circulation, where it can be measured by a commercially available ELISA kit. KL-6 has been studied extensively in mainly Japanese patients, where serum levels were found to be increased in various interstitial lung diseases such as radiation pneumonitis [22-24], CTD-associated lung disease [25-27] and drug induced pneumonitis [28]. Interestingly, KL-6 may have a role in fibrosis itself, as it was shown to induce proliferation of lung fibroblasts in vitro [29].

In 21 patients with IPF, serum KL-6 was elevated compared to healthy controls and patients with bacterial pneumonia, but not significantly different from patients with CTD-associated ILD [30]. In a 1998 study of 14 Japanese patients with rapidly progressive IPF, a diminishing KL-6 level in response to steroid pulse therapy was associated with increased survival 6 months after start of therapy [31]. However in this study, predating the 2002 ATS/ERS classification on ILD, the diagnosis of IPF was made based on HR-CT and transbronchial biopsies in 9 out of 14 patients. It is therefore very well possible that some of these patients would at present be diagnosed differently, e.g. with a NSIP. Kuwano et al. reported

increased KL-6 levels in IPF patients with signs of disease progression in the previous three months, compared to stable IPF patients [32]. Again, as this study was performed prior to 2002, one should bear in mind that the diagnosis of IPF was since then reclassified [1]. Satoh *et al.* reported an increased mortality in patients with an IIP, including patients with IPF, with serum levels of KL-6 > 1000 U/ml at initial measurement [33]. Furthermore, Yokoyama *et al.* reported worse survival of IPF patients with KL-6 levels > 1000U/ml at time of presentation, in a retrospective study of a total of 27 patients [34]. Elevated KL-6 levels have also been associated with NSIP. In fibrotic NSIP, KL-6 was elevated and correlated with the extent of fibrotic abnormalities on HRCT [35]

3.3 Surfactant Proteins

SP-A and SP-D, water-soluble members of the C-type lectin superfamily, are produced in the lung primarily by alveolar epithelial type II cells and are important constituents of the innate immunity of the lung. Gene expression profiling of lung biopsies from patients with IPF showed upregulation of the SP-A1 gene [12]. Serum levels of SP-A and SP-D are increased in IPF, but also other pulmonary diseases, probably due to type II pneumocyte hyperplasia and/or epithelial barrier breakdown [36-41]. Surfactant proteins may play a role in IPF pathogenesis themselves. Aberrant surfactant protein processing by the endoplasmic reticulum has been implicated in IPF pathogenesis and genetic defects in SP-A2 were associated with familial IPF [42-43].

Serum SP-A and SP-D levels were found to be elevated in a total of thirty-one patients with an idiopathic UIP or NSIP on lung biopsy, compared to healthy controls. In patients with a UIP pattern the SP-A levels were significantly higher compared to patients with a NSIP [40]. In a group of seven asymptomatic patients with signs of early pulmonary fibrosis in the posterior subpleural region on CT scanning, increased levels of serum SP-A and SP-D were detected [44]

Kinder *et al.* found that high levels of SP-A at time of initial diagnosis was a strong predictor of mortality in a well defined group of 82 patients with IPF. Furthermore, a model using baseline serum SP-A and SP-D provided substantial additive predictive value and was superior to a model based on clinical parameters alone [45].

3.4 CD28

There is evidence for a role for (auto-)antigen-driven immune reactions in IPF. CD4+ T cells from IPF patients show characteristics of an autoreactive immune process, and an autoreactive T cell response, due to mutations in the autoimmune regulator gene, is associated with the development of interstitial lung disease [46-47]. Furthermore, an association was found between exacerbations of IPF and a reaction to auto-antigens [48]. Similar to several auto-immune diseases, a diminished number and T cell-suppressive function of CD4+CD25+FOXP3+ regulatory T cells was found in BAL and peripheral blood from patients with IPF [49]. These data strengthen the idea that IPF is in part an antigen-driven

autoreactive immune disease. CD28 is a co-stimulatory molecule expressed on the surface of nearly all CD4+ T cells of healthy individuals that is downregulated upon repeated cycles of antigen-driven T cell proliferation. Patients with IPF with an unusually large proportion of peripheral CD4+ T-cells with downregulated CD28 were found to have a higher likelihood of requiring lung transplantations within the year [50].

3.5 Circulating fibrocytes

The accumulation of myofibroblasts in fibroblast foci, characteristic for IPF but also observed in other ILDs, was until recently thought to arise from resident fibroblast transforming into myofibroblasts or from epithelial–mesenchymal transition. More recently, circulating fibrocytes have been implicated in the pathogenesis of IPF. In a murine model for pulmonary fibrosis, circulating bone marrow-derived fibroblast precursors, called fibrocytes, were demonstrated to be attracted to the lung where they differentiated into spindle-shaped fibroblast-like cells. Circulating fibrocytes are thought to be progenitors for fibroblasts participating in the pathogenesis of lung fibrosis [51-52]. Fibrocyte precursors appear to differentiate from a subpopulation of CD14+ peripheral blood monocytes. Fibrocytes express markers of both hematopoietic cells (CD45, MHC class II, CD34) and stromal cells (collagen-I, collagen-III, and fibronectin). Homing of fibrocytes to the lung is possibly regulated by the CXCR4–CXCL12 axis [53-54].

Moeller et al. found increased proportions of circulating fibrocytes (avg. 2.72% of peripheral blood leukocytes) in a cohort of fifty-eight patients with IPF, compared to healthy controls (avg. 1%). During an acute exacerbation of IPF, observed in seven of these patients, significantly increased numbers of fibrocytes were observed. In the three patients that recovered from such an episode, the proportion of fibrocytes subsequently decreased considerably after several months. A proportion of more than 5% fibrocytes of peripheral blood leukocytes was associated with increased mortality in these patients, while PFTs and 6MWD were not [55].

3.6 Angiogenesis related biomarkers: VEGF and IL-8

Angiogenesis is thought to play a vital role in the pathogenesis of IIPs. In IPF, an increase in capillaries was found in non-fibrotic UIP lesions. Alveolar epithelial type II cells near these vessels produced the potent angiogenic factors VEGF and IL-8 [56]. In a study of forty-nine patients with IIP, including thirty-nine patients with IPF, baseline levels of plasma IL-8, but not VEGF, were significantly higher compared to controls. A subgroup of patients with progressive disease had higher baseline levels of IL-8 and VEGF, compared to stable patients, and IL-8 and VEGF levels were correlated to amount of fibrosis on HRCT at baseline [57]. Ando et al. recently reported that within a group of forty-one patients with IPF, serum VEGF was increased in patients with a high alveolar–arterial difference of oxygen, and correlated to KL-6 levels and interstitial abnormalities on HRCT [58].

3.7 MMPs

Matrix degrading enzymes of the MMP family are thought to be critically involved in the deposition and remodeling of the extracellular matrix, as observed in pulmonary fibrosis [59-61]. A genetic polymorphism in the MMP1 promotor was linked to IPF in smoking individuals [62]. Rosas et al. simultaneously analyzed forty-nine different serum markers and found five MMPs among the twelve proteins differentially expressed in serum from patients with IPF. MMP1 and MMP7 levels were most clearly increased in plasma from patients with IPF, but not in patients with sarcoidosis or COPD, and MMP1 and MMP7 expression was furthermore enhanced in lung tissue and BAL [63]. Plasma MMP1 and MMP7 levels were significantly higher in IPF patients than in patients with HP, in agreement with MMP1 and MMP7 gene expression data from lung biopsies [11]. Interestingly, in patients with asymptomatic IPF enhanced levels of MMP7 were found, although lower than in symptomatic patients, indicating that MMP7 may serve as a marker for early disease and disease progression [63]. It is unlikely that MMP7 will serve as a biomarker distinguishing between IPF and NSIP, as enhanced levels of MMP7 were found in the BAL of patients with NSIP [64].

3.8 Oxidative stress biomarkers

Oxidative stress may play a role in the epithelial dysfunction underlying pulmonary fibrosis; an increased production of oxidants is thought to be involved in epithelial cell apoptosis and dysregulated repair [16]. Indeed, the oxidant burden in the lungs of patients with pulmonary fibrosis was found to be increased [65-66] and increased levels of H₂O₂ and 8-isoprostane were found in the exhaled breath condensate of IPF patients [67]. Furthermore, in animal models for pulmonary fibrosis defective anti-oxidant mechanisms resulted in augmented fibrosis [16]. A role for oxidative stress in the pathogenesis of IPF is perhaps also supported by the results from the IFIGENIA trial, where the favorable effect of treatment have been attributed to N-acetylcysteine, an anti-oxidant [68]. Measuring serum hydroperoxides, using a commercially available method, Daniil et al. found enhanced levels of systemic oxidative stress in patients with IPF, compared to age-matched healthy controls, correlating with dyspnea. Furthermore, the levels of systemic oxidative stress showed an inverse correlation with both lung volume and diffusion capacity [69].

4 Discussion

Biomarkers are a potentially valuable tool in diagnosing and treating patients with an IIP. However, in general the biomarkers described have several drawbacks. (1) Their specificity for a single interstitial lung disease is poor, in most cases several other diseases can cause an increase in any of these markers. (2) The biomarkers investigated have usually been tested in limited numbers of patients in a retrospective fashion and have not been validated prospectively. Validation of new biomarkers can be

further hampered by the absence of a diagnostic 'gold standard', as described above. (3) At present, it is unclear to what extent the biomarkers investigated will contribute to data already obtained and used in every day clinical practice such as 6 minute walking distance, pulmonary function tests, pulmonary artery pressure, histopathology and HR-CT characteristics [70-71]. For example, KL-6 seems to be a good surrogate marker for pulmonary fibrosis, but thus far cannot replace conventional diagnostic procedures. Remarkably, in Japan this marker has already found its way into everyday practice, perhaps reflecting the extensive experimental experience with this biomarker [72].

Several serum biomarkers derive from proliferating epithelial cells and/or disruption of the epithelial barrier. A major concern, that has not been fully addressed, is the possibility that enhanced levels of some of these biomarkers can be found in IIPs as well as in malignancies, while these diseases may very well coincide. For example, an increased incidence of IPF has been reported in patients with hepatitis C virus (HCV) infection [73-74]. Arase et al. reported increased levels of KL-6 one year before clinical onset of IPF in HCV patients [75]. However, in a later report increased levels of KL-6 were mainly associated with the development of hepatocellular carcinoma in HCV patients [76]. In addition, KL-6 concentrations can be increased in patients with other malignancies, such as adenocarcinoma of the lung, breast or pancreas [76-77]. This may be a confounding factor in the investigations into KL-6 as a biomarker for prognosis of IPF, as IPF itself is associated with an increased incidence of lung cancer, raising the question whether the correlation between increased levels of KL-6 and a worse prognosis of IPF patients is partly due to an increase in lung cancer [78-80]. Similarly, serum VEGF levels were not only reported to be increased in advanced stages of pulmonary fibrosis, but also significantly increased in lung cancer patients [81].

5 Future perspective

It is unlikely that a single biomarker will become a valuable diagnostic tool. A composite of several biomarkers holds promise. Combining measurement of five serum proteins, including three MMPs, could correctly differentiate between IPF patients and controls, with a with a sensitivity of 98.6% and specificity of 98.1% [63]. Simultaneous analysis of 17 serum proteins, using Luminex bead technology, correctly differentiated between healthy controls, patients with sarcoidosis and systemic sclerosis patients in 90% of cases [82]. We feel that further research into such composite markers, especially within the group of sometimes difficult to diagnose IIPs, is warranted.

Separate serum biomarkers do show potential in aiding clinical decision making. However, currently validation of the clinical applicability of biomarkers in IIPs is insufficient. Circulating fibrocytes may become an interesting biomarker for IPF, as they not only may indicate disease progression but also form a target for therapy [55, 83]. Serum amyloid P (SAP), a naturally occurring plasma protein involved in wound repair, was found to inhibit fibrocyte formation and regulate the activity of innate immune cells in response to injury [84-85]. In mice, injection of SAP reduced bleomycin-induced pulmonary fibrosis [52]. However, in humans phase I studies with SAP have only recently been initiated. Validation

of the usefulness of fibrocytes as a biomarker hopefully comes from ancillary data from the PANTHER trial [83].

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