

## HOW TO BUILD A BIOMARKER: IL-7 AND ACUTE EXACERBATION OF IPF

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In this issue of *Sarcoidosis Vasculitis and Diffuse Lung Diseases*, Tachibana et al evaluate several serum cytokines and chemokines as possible prognostic biomarkers in acute exacerbation of idiopathic pulmonary fibrosis (1). They report that change in circulating serum IL-7 level after treatment with polymyxin B direct hemoperfusion is an independent predictor of survival time in this population.

The Federal Drug Administration broadly defines a biomarker as a “measurable characteristic that can be used as an indicator of a particular disease or some other physiological state of an organism” (2). We most commonly think of a biomarker as a blood or serum test, but in fact it can be any subjective or objective measurement. A clinically useful biomarker must measure and provide information regarding diagnosis, disease severity, treatment responsiveness, or prognosis, and ideally would inform a combination of these factors. In addition, clinically useful biomarkers should provide information beyond that obtained from other common and easily measured variables already used by clinicians.

The ideal prognostic biomarker would not just predict outcome, but would also be sensitive to interventions (such as polymyxin B direct hemoperfusion) that might affect that outcome; i.e. it would be a validated surrogate. In such a case, effective therapies would change the biomarker’s level, and improvement in that biomarker would correlate with improvement in the outcome of interest (e.g. breathlessness or survival). The two most commonly used prognostic biomarkers in IPF are the forced vital capacity (FVC) and diffusion capacity for carbon monoxide (DLCO); neither of these is a validated

surrogate but baseline values and changes in values over time have been correlated with survival (3-6). Unfortunately, while a few potential blood-based prognostic biomarkers (e.g. KL-6, MMP-7 and CCK18) have recently been described, there is currently no blood biomarker central to IPF management or prognostication.

A candidate prognostic biomarker must undergo rigorous testing prior to clinical use. First, the derivation study must be well constructed and internally valid, with an appropriate and reproducible study design. Subject selection must be transparent, and specimen collection, handling, and methods of biomarker analysis must all be standardized. Second, preliminary findings must be externally validated in a second study performed in an independent population. This essential step protects against error and multiple forms of bias that may have influenced the results of the initial study. If validated, the final step would be to test whether measuring the biomarker actually improves prognostication in clinical practice. Ideally, patients would be randomized to having the biomarker measured or not, and the accuracy of prognosis would be compared between the two groups.

Interleukin (IL)-7 is not an unreasonable candidate prognostic biomarker in acute exacerbation of IPF. IL-7 is critical for maturation and proliferation of B and T cells, helps maintain lymphocyte homeostasis, and modulates immune responses to several stimuli (7). It is produced by several epithelial cell types (7), however IL-7 production in alveolar epithelial cells has not been clearly established. Although IL-7 is generally considered an im-

munomodulatory cytokine, it may have antifibrotic effects as well. IL-7 has been shown to inhibit TGF-beta production and signaling in vitro and recombinant IL-7 reduced pulmonary fibrosis in a bleomycin mouse model (8). The results of the present study suggest that an increase in serum IL-7 after polymyxin B direct hemoperfusion predicts improved survival from acute exacerbation, which could be explained by its antifibrotic properties.

Although intriguing, it is important to realize that this study represents just the first step in the evaluation of IL-7 as a potential prognostic biomarker in acute exacerbation of IPF. These results will need to be validated in a second, distinct cohort of patients, and the relevance of a change in IL-7 absent polymyxin B direct hemoperfusion will have to be investigated. Further, the additive prognostic utility of change in serum IL-7 level to other prognostic measures in acute exacerbation (e.g. presence of mechanical ventilation, extent of ground glass abnormality on CT scan) will have to be demonstrated. The impact of potential therapies for acute exacerbation on the change in IL-7 level should also be determined, and the validity of change in IL-7 as a surrogate marker of clinical outcomes assessed.

These additional steps are essential in helping clinicians decide about incorporating serum IL-7 measurement into clinical practice.

## References

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