Do Circulating Monocytes Promote and Predict IPF Progression?

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Despite the availability of pharmacologic therapies, idiopathic pulmonary fibrosis (IPF) is still a clinical challenge. It is a lethal disease with a clinical course that cannot be predicted at the time of diagnosis. The high burden of suffering in IPF, the need to prioritize a select few for transplantation, and the high mortality of IPF highlight the need for better, simpler, and clinically applicable prognostic tools. In airways disease, for example(1, 2) , eosinophil counts are routinely used for subphenotyping, directed therapy, and assessment of therapy responses. Is there an IPF equivalent to eosinophils?

Growing evidence supports that innate and adaptive immune cells disrupt normal lung repair. Some key studies have brought to light that several circulating immune populations have the potential to reflect and predict disease outcome either by RNA(3), protein(4) or cellular counts(5). Scott and colleagues(5), by performing cell deconvolution analysis of transcriptome data, reported an unexpected finding of an association between absolute and relative numbers of circulating monocytes and survival in individuals with idiopathic pulmonary fibrosis. In their study, patients with high monocyte counts were at higher risk for poor outcomes. Monocyte counts of 0.95 GI/L or greater were associated with mortality after adjusting for forced vital capacity (FVC), gender, age, and physiology index. These associations were validated in 7000 IPF patients through five different cohorts.

Supporting these findings, here, Kreuter and colleagues(6) performed a retrospective pooled analysis in 2067 patients from randomized double blinded phase III studies (ASCEND(7), CAPACITY(8), and INSPIRE(9)), to determine whether monocyte count at baseline were associated with IPF progression. The determinants of progression were defined as ≥10% absolute decline in percent predicted FVC, ≥50 m decline in 6-minute walk distance (6MWD), all-cause hospitalization, and all-cause mortality over 1 year. The differential blood counts

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used for the analysis were pooled data from routine assessment at local institutions. In addition to a monocyte count higher than 0.95 GI/L, which was investigated in Scott et al(5), Kreuter et al found that monocyte counts higher than 0.95 GI/L and that lower counts between 0.60 and 0.95 GI/L were associated with worse 1-year outcomes. Elevated monocyte counts of 0.60–0.95 and >0.95 GI/L were associated with significantly increased risks of IPF progression, hospitalization, and mortality over 1 year. This persisted also after adjustment for demographics, physiologic function, comorbidity profile, and chronic immunosuppressant use. Dynamic changes in monocyte counts were, however, not associated with outcomes, and antifibrotic treatments were not associated with significant changes in monocyte counts.

Validation of the prior Scott study by Kretuer and colleagues should bolster our collective confidence that monocyte counts do indeed track with mortality. Assessing the performance of monocyte counts needs to be considered in the context of other leukocyte lineages counts. Here, the authors observed, as with monocytes, that a high neutrophil count was associated with a higher risk of worse outcomes and a high lymphocyte counts with lower risk of worse outcomes. These data suggest all sorts of questions. From the data presented in this study several questions arise, what is the precise role of monocytes in disease? Can monocyte reflect response to treatment? Are lymphocytes “good” and monocytes (and neutrophils) “bad”? Can elevated monocyte counts predict patients at risk of acute exacerbations? Can monocyte counts sub-phenotype IPF patients? And how do monocyte counts perform when compared with other already biomarkers in IPF?

The data used for the analysis were differential blood counts measured by routine laboratory testing. This argues that clinical implementation of monocyte counts as predictive of IPF prognosis, if further validated, would be easy. Complete blood counts are, however, unable to

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differentiate between progenitor and immature monocytes, monocyte subtypes, or myeloid-derived monocyte-like cells, all phenotypically alike. Perhaps one of these subtypes is the pathologic actor? This is an important question because cells from the myeloid lineage, immature progenitors and end-differentiated cells, circulating in the peripheral blood may be implicated in the pathogenesis and prognostic in IPF. Fibrocytes are matrix-producing, bone-marrow derived monocyte-like cells that are increased in stable IPF and during acute exacerbations(10). Initial indications also demonstrate that Myeloid-derived suppressor cells, a population of early released immature monocyte progenitors, are abundant in the peripheral blood and might contribute to disease and reflect progression(11). CC-chemokine Ligand 18 (CCL18) secreted by activated human myeloid cells was reported as soluble serum biomarker to predict mortality in IPF(12). Single cell RNA sequencing studies have allowed unbiased, high-throughput, and high-resolution views of individual cell compartments in the IPF lung. These studies have identified heterogeneous myeloid subpopulations of monocytes, macrophages, dendritic cells that uniquely emerge during lung fibrosis(13-15) . Now, the data from Scott and now from Kreuter from patients with IPF underscore the critical importance of inflammation in this disease. These findings reveal that peripheral blood myeloid cells have the potential to not only predict disease outcome, but also to reveal active disease processes in the lung. Whether there is an etiological role for monocytes in IPF, or whether they can alter the natural history of IPF, are fundamental questions that still need to be conclusively answered. Even considering early decision making for antifibrotic therapy initiation or pre-transplant evaluation in patients with high monocyte counts, may not be far off. Hence, more studies that explore in depth the mechanistic role of monocytes in lung fibrosis are urgently required.

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Another important aspect to emphasize here is how large IPF clinical trials are equipped to address biological and mechanistic questions. Ancillary studies from large clinical trials, as both Scott and Kreuter and colleagues have now shown, are highly valuable treasures that should serve to advance, from multiple angles, the knowledge in the field. Unquestionably, the results presented in this study, we hope, will generate enthusiasm towards validation of monocytes as a biomarker and implementation of monocyte count to answer the questions that vex us as providers who care for patients with IPF.

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