be the decision to proceed with transplant listing and surgery, as survival with advanced CF lung disease on ETI will undoubtedly improve, allowing individuals to safely delay transplant. As additional data accumulate to provide clarity on best practices, individuals with CF, their families, and providers should continue to celebrate the transformative impact of CFTR modulators on quality of life and survival. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Mike Myerburg, M.D.
Joseph M. Pilewski, M.D.
Division of Pulmonary, Allergy, and Critical Care Medicine
University of Pittsburgh
Pittsburgh, Pennsylvania

ORCID ID: 0000-0002-0893-1155 (J. M.P.).

References

1. Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Dřevínek P, *et al.*; VX08-770-102 Study Group. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. *N Engl J Med* 2011;365: 1663–1672.
2. Barry PJ, Plant BJ, Nair A, Bicknell S, Simmonds NJ, Bell NJ, *et al.* Effects of ivacaftor in patients with cystic fibrosis who carry the G551D mutation and have severe lung disease. *Chest* 2014;146:152–158.
3. Polenakovik HM, Sanville B. The use of ivacaftor in an adult with severe lung disease due to cystic fibrosis (ΔF508/G551D). *J Cyst Fibros* 2013; 12:530–531.
4. Taylor-Cousar J, Niknian M, Gilmartin G, Pilewski JM; VX11-770-901 investigators. Effect of ivacaftor in patients with advanced cystic fibrosis and a G551D-CFTR mutation: safety and efficacy in an expanded access program in the United States. *J Cyst Fibros* 2016;15:116–122.
5. Salvatore D, Terlizzi V, Francalanci M, Taccetti G, Messore B, Biglia C, *et al.* Ivacaftor improves lung disease in patients with advanced CF carrying CFTR mutations that confer residual function. *Respir Med* 2020;171: 106073.
6. Keating D, Marigowda G, Burr L, Daines C, Mall MA, McKone EF, *et al.*; VX16-445-001 Study Group. VX-445-Tezacaftor-Ivacaftor in patients with cystic fibrosis and one or two Phe508del alleles. *N Engl J Med* 2018; 379:1612–1620.
7. Middleton PG, Mall MA, Dřevínek P, Lands LC, McKone EF, Polineni D, *et al.*; VX17-445-102 Study Group. Elexacaftor-tezacaftor-ivacaftor for cystic fibrosis with a single Phe508del allele. *N Engl J Med* 2019;381: 1809–1819.
8. Heijerman HGM, McKone EF, Downey DG, Van Braeckel E, Rowe SM, Tullis E, *et al.*; VX17-445-103 Trial Group. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial. *Lancet* 2019;394:1940–1948.
9. O'Shea KM, O'Carroll OM, Carroll C, Grogan B, Connolly A, O'Shaughnessy L, *et al.* Efficacy of elexacaftor/tezacaftor/ivacaftor in patients with cystic fibrosis and advanced lung disease. *Eur Respir J* 2021;57:2003079.
10. Burgel P-R, Durieu I, Chiron R, Ramel S, Danner-Boucher I, Prevotat A, *et al.*; French Cystic Fibrosis Reference Network study group. Rapid improvement after starting elexacaftor–tezacaftor–ivacaftor in patients with cystic fibrosis and advanced pulmonary disease. *Am J Respir Crit Care Med* 2021;64–73.
11. Higgins M, Volkova N, Moy K, Marshall BC, Bilton D. Real-world outcomes among patients with cystic fibrosis treated with ivacaftor: 2012-2016 experience. *Pulm Ther* 2020;6:141–149.
12. Volkova N, Moy K, Evans J, Campbell D, Tian S, Simard C, *et al.* Disease progression in patients with cystic fibrosis treated with ivacaftor: data from national US and UK registries. *J Cyst Fibros* 2020;19:68–79.
13. Ramos KJ, Smith PJ, McKone EF, Pilewski JM, Lucy A, Hempstead SE, *et al.*; CF Lung Transplant Referral Guidelines Committee. Lung transplant referral for individuals with cystic fibrosis: Cystic Fibrosis Foundation consensus guidelines. *J Cyst Fibros* 2019;18:321–333.
14. Ramos KJ, Quon BS, Heltshe SL, Mayer-Hamblett N, Lease ED, Aitken ML, *et al.* Heterogeneity in survival in adult patients with cystic fibrosis with FEV1 $<$ 30% of predicted in the United States. *Chest* 2017;151:1320–1328.

Copyright © 2021 by the American Thoracic Society

Check for updates

Do Circulating Monocytes Promote and Predict Idiopathic Pulmonary Fibrosis Progression?

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 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 IPF. In their study, patients with high monocyte counts were at higher risk for poor outcomes. Monocyte counts of 0.95×10^9/L or greater were associated with mortality after adjusting for FVC, sex, age, and physiology index. These associations were validated in 7,000 patients with IPF through five different cohorts.

This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0 (https://creativecommons.org/licenses/by-nc-nd/4.0/). For commercial usage and reprints, please contact Diane Gern (dgern@thoracic.org).

Originally Published in Press as DOI: 10.1164/rccm.202101-0207ED on February 24, 2021

Supporting these findings, in this issue of the *Journal*, Kreuter and colleagues (pp. 74–81) (6) performed a retrospective pooled analysis in 2,067 patients from randomized double blinded phase III studies, ASCEND (Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis) (7), CAPACITY (Clinical Studies Assessing Pirfenidone in IPF: Research of Efficacy and Safety Outcomes) (8), and INSPIRE (Effect of Interferon gamma-1b on Survival in Patients with Idiopathic Pulmonary Fibrosis) (9), to determine whether monocyte count at baseline was associated with IPF progression. The determinants of progression were defined as $\geq$10% absolute decline in percent predicted FVC, $\geq$50 m decline in 6-minute-walk distance, all-cause hospitalization, and all-cause mortality over 1 year. The differential blood counts used for the analysis were pooled data from routine assessment at local institutions. In addition to a monocyte count higher than 0.95×10^9/L, which was investigated in Scott and colleagues (5), Kreuter and colleagues found that monocyte counts higher than 0.95×10^9/L and lower counts between 0.60 and 0.95×10^9/L were associated with worse 1-year outcomes. Elevated monocyte counts of 0.60–0.95 and $>0.95\times10^9$/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 lineage 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 count with lower risk of worse outcomes. These data raise all sorts of questions. What is the precise role of monocytes in disease? Can monocyte counts 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 subphenotype patients with IPF? And how do monocyte counts perform when compared with other 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 differentiate between progenitor and immature monocytes, monocyte subtypes, or myeloid-derived monocyte-like cells, all phenotypically alike. Is, perhaps, one of these subtypes 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). CCL18 (CC-chemokine ligand 18) secreted by activated human myeloid cells was reported as a 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, and dendritic cells that uniquely emerge during lung fibrosis (13–15). The data from Scott and colleagues, and now from Kreuter and colleagues, underscore the critical importance of inflammation in IPF. 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 pretransplant 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.

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 colleagues 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 toward 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. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Isis E. Fernandez, M.D., Ph.D.
Department of Internal Medicine V, University Hospital, LMU, Munich, Germany
and
Helmholtz Center Munich, Ludwig-Maximilians-University Munich, Munich, Germany

Daniel J. Kass, M.D.
Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania

ORCID ID: 0000-0001-6597-7830 (D.J.K.).

References

1. Price DB, Rigazio A, Campbell JD, Bleecker ER, Corrigan CJ, Thomas M, *et al.* Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study. *Lancet Respir Med* 2015;3:849–858.
2. Watz H, Tetzlaff K, Wouters EF, Kirsten A, Magnussen H, Rodriguez-Roisin R, *et al.* Blood eosinophil count and exacerbations in severe chronic obstructive pulmonary disease after withdrawal of inhaled corticosteroids: a post-hoc analysis of the WISDOM trial. *Lancet Respir Med* 2016;4: 390–398.
3. Herazo-Maya JD, Sun J, Molyneaux PL, Li Q, Villalba JA, Tzouvelekis A, *et al.* Validation of a 52-gene risk profile for outcome prediction in patients with idiopathic pulmonary fibrosis: an international, multicentre, cohort study. *Lancet Respir Med* 2017;5:857–868.
4. Yokoyama A, Kohno 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;158:1680–1684.

5. Scott MKD, Quinn K, Li Q, Carroll R, Warsinske H, Vallania F, *et al.* Increased monocyte count as a cellular biomarker for poor outcomes in fibrotic diseases: a retrospective, multicentre cohort study. *Lancet Respir Med* 2019;7:497–508.
6. Kreuter M, Bradley SJ, Lee JS, Tzouvelekis A, Oldham JM, Molyneaux PL, *et al.* Monocyte count as a prognostic biomarker in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2021;203;74–81.
7. King TE Jr, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, *et al.*; ASCEND Study Group. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 2014;370:2083–2092.
8. Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, *et al.*; CAPACITY Study Group. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet* 2011; 377:1760–1769.
9. King TE Jr, Albera C, Bradford WZ, Costabel U, Hormel P, Lancaster L, *et al.*; INSPIRE Study Group. Effect of interferon gamma-1b on survival in patients with idiopathic pulmonary fibrosis (INSPIRE): a multicentre, randomised, placebo-controlled trial. *Lancet* 2009;374:222–228.
10. Moeller A, Gilpin SE, Ask K, Cox G, Cook D, Gauldie J, *et al.* Circulating fibrocytes are an indicator of poor prognosis in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2009;179:588–594.
11. Fernandez IE, Greiffo FR, Frankenberger M, Bandres J, Heinzelmann K, Neurohr C, *et al.* Peripheral blood myeloid-derived suppressor cells reflect disease status in idiopathic pulmonary fibrosis. *Eur Respir J* 2016; 48:1171–1183.
12. Prasse A, Probst C, Bargagli E, Zissel G, Toews GB, Flaherty KR, *et al.* Serum CC-chemokine ligand 18 concentration predicts outcome in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2009;179:717–723.
13. Reyfman PA, Walter JM, Joshi N, Anekalla KR, McQuattie-Pimentel AC, Chiu S, *et al.* Single-cell transcriptomic analysis of human lung provides insights into the pathobiology of pulmonary fibrosis. *Am J Respir Crit Care Med* 2019;199:1517–1536.
14. Morse C, Tabib T, Sembrat J, Buschur KL, Bittar HT, Valenzi E, *et al.* Proliferating SPP1/MERTK-expressing macrophages in idiopathic pulmonary fibrosis. *Eur Respir J* 2019;54:1802441.
15. Adams TS, Schupp JC, Poli S, Ayaub EA, Neumark N, Ahangari F, *et al.* Single-cell RNA-seq reveals ectopic and aberrant lung-resident cell populations in idiopathic pulmonary fibrosis. *Sci Adv* 2020;6:eaba1983.

Copyright © 2021 by the American Thoracic Society

Check for updates

Baby's First Cries and Establishment of Gas Exchange in the Lung

In this issue of the *Journal*, the report from Tingay and colleagues (pp. 82–91) about the behavior of gases in the term infant lung presents new information about the initial aeration to air-breathing in a Cesarean section–delivered healthy term newborn who did not require any respiratory assistance (1). It builds on recent interest in how to aerate the newborn lung to minimize injury (2, 3). The initial aeration of the fluid-filled lung is perhaps the largest physiologic challenge for all mammals because other fetal organs that must work and are essential for fetal survival have been tested *in utero*. During the fetal period, poor cardiac function results in hydrops or intrauterine demise, impaired renal function leads to oligohydramnios and pulmonary hypoplasia, and disordered brain function can lead to contractures and arthrogryposis. The lung transition requires respiratory challenges and, as we are learning, elaborate coordination of pharyngeal reflexes to support airway patency and mechanisms to rapidly move the fetal lung fluid out of the airspace and into the interstitium of the lung and ultimately out of the lung (4). The fetal lung is not collapsed (Figure 1A): it has a normal FRC of about 30 ml/kg maintained by low protein content fluid (5).

The new information provided by Tingay and colleagues using breath-by-breath electrical impedance tomography shows that as the infants are transitioning to air-breathing, they have two distinct breathing patterns: crying and tidal breathing. Crying is the primary breathing that recruits FRC, which is achieved within 43 breaths (1). The initial gas flow goes primarily into the right lung to nondependent sections and is nonuniform (Figure 1B). Crying is associated with the expiratory braking of flow, which redistributes gas in the lung by pendelluft flow to preserve FRC (Figure 1C). These are unique patterns of breathing and gas flow that probably occur only during the neonatal transition to air-breathing. Inflation of the lungs also contributes to lung liquid clearance (6).

Do the results provide clinical insights to help guide strategies to assist the transition to air-breathing when assistance is needed? There recently has been great interest in how best to use continuous positive airway pressure to optimize aeration of the preterm usually surfactant-deficit infants to avoid pressure-related lung injury using sustained inflation (7). A recent randomized control trial of sustained inflation was stopped because of increased death in the intervention group. The cause of increased death in the sustained inflation group was not known (2). The results of Tingay and colleagues may provide a clue because of the preferred flow of gas to the nondependent lung regions, which could cause localized overinflation and injury. We have a bad habit of applying interventions to neonatal care before we understand the normal physiology. Tingay and colleagues have provided us with information about normal transition gas volumes to develop different, innovative strategies that might be more aligned with normal transitional physiology. There is other recent information about the complex gene expression changes in the lung around the transition to air-breathing (8). There was mRNA expression heterogeneity in lung cell type RNA, indicating cell stress and unfolded protein responses. The remarkable result using electrical impedance tomography is how rapidly the FRC is established. Some of the values are quite high, suggesting that there might be gas trapping.

Tingay and colleagues (1) have provided us with new information about $\dot{V}$ (ventilation with gas) but no information about $\dot{Q}$ (pulmonary blood flow). Hypoxic pulmonary vasoconstriction contributes to high fetal pulmonary vascular resistance, and ventilation with air or oxygen reduces pulmonary vascular resistance (9, 10). The infants in the study by Tingay and colleagues had gradually improving oxygenation from their initial median oxygen saturation as measured by pulse oximetry (Sp_{O_2}) of about 52% at 60 seconds to 78% by 360 seconds, so presumably, at least initially, there was diversion of pulmonary blood flow away from

This article is open access and distributed under the terms of the Creative Commons Attribution Non-Commercial No Derivatives License 4.0 (https://creativecommons.org/licenses/by-nc-nd/4.0/). For commercial usage and reprints, please contact Diane Gern (dgern@thoracic.org).

Originally Published in Press as DOI: 10.1164/rccm.202102-0308ED on March 8, 2021