IL-1 Blockade Reduces Inflammation in Pulmonary Arterial Hypertension and Right Ventricular Failure: A Single-Arm, Open-Label, Phase IB/II Pilot Study

To the Editor:

Over time, patients with longstanding pulmonary arterial hypertension (PAH) experience pressure overload in the right ventricle (RV), leading to reduced contractile force and chamber dilation. Present strategies to treat PAH consist of pulmonary arterial vasodilators by way of the prostacyclin, endothelin, or nitric oxide pathways. It is now appreciated that maladaptive inflammatory signaling is a key contributor to the development of obliterative pulmonary arteriolar lesions and RV failure in PAH (1, 2), and that IL-1 and IL-6 levels correlate with the degree of RV failure (3).

With experimental animal data suggesting anakinra (recombinant IL-1 receptor antagonist) protects against development of PAH (4), we designed a single-group, open-label phase IB/II pilot study (clinicaltrials.gov identifier: NCT03057028) to evaluate the feasibility and safety of treatment with anakinra as add-on therapy to standard of care in patients with stable PAH and RV failure. In addition to the preclinical data, anakinra was chosen on the basis of multiple favorable clinical trials in left-sided systolic dysfunction by our group (5, 6).

Here we report the findings from our pilot study. From October 2017 to May 2018, patients at the Virginia Commonwealth University treated for pulmonary hypertension were screened for eligibility. Inclusion criteria included group 1 PAH (7) (not associated with connective tissue disease, human immunodeficiency virus, portal hypertension, or schistosomiasis), age >18 years, and symptomatic RV failure (objective findings of RV dysfunction by echocardiography [RV diastolic diameter >4.3 cm, fractional area change <35%, or tricuspid annular plane systolic excursion ⩽1.5 cm] with New York Heart Association class II or III heart failure symptoms) despite optimal PAH therapy. Exclusion criteria included autoimmune/autoinflammatory diseases, anti-inflammatory medications, recent malignancy or infection, and severe renal dysfunction. Of the 39 patients who met inclusion criteria, 10 were excluded (chronic inflammatory disorders [$n = 4$], infection [$n = 1$], severe renal dysfunction [$n = 2$], non–English speaking [$n = 1$], unable to consent [$n = 1$], pregnant [$n = 1$]). Sixteen patients were approached for the study: 6 declined to participate, and 10 agreed to enroll, which was the sample size chosen to gather preliminary data. However, scheduling conflicts prevented two patients from completing baseline testing, and one patient was hospitalized for urosepsis before enrollment. Thus, seven patients were enrolled in the study, in which they provided signed consent (approved by the institutional review board) and received anakinra 100 mg subcutaneously daily for 14 days, which is the dose approved by the U.S. Food and Drug Administration for the treatment of rheumatoid arthritis. Baseline testing before treatment included biomarkers (high-sensitivity C-reactive protein [hsCRP], IL-6, and N-terminal pro B-type natriuretic peptide [NT-proBNP]), quality-of-life questionnaires (Duke Activity Severity Index and Minnesota Living with Heart Failure Questionnaire), transthoracic echocardiography, and cardiopulmonary exercise testing for measurement of peak oxygen consumption and ventilatory efficiency ($\dot{V}_E$:$\dot{V}_{CO_2}$ slope) (8). All tests were repeated at Day 14 of treatment, in addition to a safety assessment. This was intended to be a safety and feasibility study, but for the purposes of designing future studies, two co–primary endpoints were specified: change in peak $\dot{V}_{O_2}$ and change in $\dot{V}_E$:$\dot{V}_{CO_2}$ slope, which were chosen because of their established reproducibility, prognostic value, and placebo-insensitive nature resulting from the open-label design of the study (9). Statistical analysis was performed with SPSS 24.0 (IBM), using the Wilcoxon test for paired data or the Spearman rank test for correlations.

Six patients completed the protocol and returned for repeat testing; they were included in the main analysis. Baseline characteristics are presented in Table 1. One patient was unwilling to return for repeat testing, and thus was not included in the main analysis but was included in the safety analysis.

No major safety events were observed during the study period. After 14 days of treatment, hsCRP levels were significantly reduced compared with baseline, with a trend toward IL-6 reduction (Figure 1). There were no significant changes from baseline in peak $\dot{V}_{O_2}$, $\dot{V}_E$:$\dot{V}_{CO_2}$ slope, exercise time, NT-proBNP, RV fractional area change, or tricuspid annular plane systolic excursion (Figure 1; all $P \geqslant 0.463$). There was a significant improvement in heart failure symptoms as assessed by the Minnesota Living with Heart Failure Questionnaire and a trend toward improvement in the Duke Activity Severity Index scores (Figure 1). Changes in hsCRP inversely correlated with changes in peak oxygen consumption ($R = -0.829$; $P = 0.046$) and Duke Activity Severity Index scores ($R = -0.845$; $P = 0.034$).

Three patients (43%) experienced minor injection site reactions. No reactions required treatment discontinuation, and all resolved spontaneously. One patient with a history of symptomatic atrial ectopy perceived a higher burden of palpitations and prematurely discontinued the treatment after 4 days; she was not willing to return for repeat testing. Another patient with a history of secondary Graves' disease had symptomatic improvement of preexisting proptosis during anakinra treatment, but subsequent progression after drug discontinuation for which she was seen by rheumatology and started on methotrexate therapy with a single dose of rituximab, with good clinical response; this was considered by the investigators to be a moderate event, and possibly related to anakinra treatment. There were no infections, hospitalizations, emergency department visits, or unplanned escalation of medical care during the study period.

The data obtained from this pilot study suggest that IL-1 blockade with anakinra in patients with PAH and RV failure is feasible and safe. Further studies are needed to validate these findings and explore the therapeutic potential of this treatment strategy. Limitations include the open-label treatment design without placebo comparison, conduct at a single center, small sample size, and the use of only one dose of anakinra

This study was supported by a grant from the VCU Johnson Center for Critical Care and Pulmonary Research and a Clinical and Translational Science Award (UL1TR000058 from the National Center for Research Resources) to the Virginia Commonwealth University Center for Clinical and Translational Research. Swedish Orphan Biovitrum LLC (Stockholm, Sweden) provided the study medication (anakinra) free of cost, but had no role in the study design, conduct, analysis, or reporting.

Author Contributions: Conception and design: C.R.T., J.M.C., A.F., B.W.V.T., A.A., and D.G.; data acquisition: C.R.T., J.M.C., D.K., R.M., H.M.D.C., J.P., A.F., B.W.V.T., A.A., and D.G.; interpretation of data: C.R.T., J.M.C., D.K., R.M., H.M.D.C., J.P., A.F., B.W.V.T, A.A., and D.G.; intellectual contributions to the manuscript: C.R.T., J.M.C., D.K., R.M., H.M.D.C., J.P., A.F., B.W.V.T., A.A., and D.G.

Originally Published in Press as DOI: 10.1164/rccm.201809-1631LE on November 12, 2018

Table 1. Individual Patient Demographics and Baseline Characteristics

Patient No.	Age (*yr*)	BMI (kg/m^2)	Sex	Ethnicity	Coexisting Conditions	Classification of PAH	Qualifying Right Heart Catheterization	Current PAH/RV Failure Treatment
1	64	16	F	W	None	Idiopathic	PA mean, 47 mm Hg PCWP, 7 mm Hg PVR, 13.3 WU	Selixipag Riociguat Ambrisentan Carvedilol Furosemide
2	75	34.5	F	B	Paroxysmal atrial fibrillation Hypertension Diabetes mellitus	Idiopathic	PA mean, 30 mm Hg PCWP, 7 mm Hg PVR, 6.6 WU	Sildenafil Oxygen Amlodipine Bumetanide
3	30	31.8	F	W	Secondary Graves' disease Supraventricular tachycardia	Idiopathic	PA mean, 49 mm Hg PCWP, 3 mm Hg PVR, 17.7 WU	Tadalafil Epoprostenol Macitentan Spironolactone Torsemide
4	83	34.4	M	B	Atrial flutter Diabetes mellitus	Idiopathic	PA mean, 46 mm Hg PCWP, 9 mm Hg PVR, 5.8 WU	Sildenafil Selixipag Oxygen Metoprolol Amlodipine Furosemide
5	71	33.8	M	B	Hypertension Diabetes mellitus Atrial fibrillation and flutter	Idiopathic	PA mean, 45 mm Hg PCWP, 15 mm Hg PVR, 4.7 WU	Treprostinil Oxygen Metolazone Carvedilol Furosemide
6	61	30.8	F	W	Hypertension Diabetes mellitus	Idiopathic	PA mean, 39 mm Hg PCWP, 13 mm Hg PVR, 6.7 WU	Sildenafil Macitentan

Definition of abbreviations: B = black; BMI = body mass index; PA = pulmonary artery; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; PVR = pulmonary vascular resistance; RV = right ventricle; W = white; WU = Wood units.

tested over a short duration. In addition, although every patient had invasive hemodynamic measurements consistent with PAH, the majority of our patients were older than 60 years with multiple risk factors for left-sided heart disease. Nonetheless, we observed a significant reduction in hsCRP in this study cohort, suggesting that the inflammatory burden in this population may be alleviated by IL-1 blockade. This reduction correlated with improvements in peak oxygen consumption during maximal effort cardiopulmonary exercise testing, as well as improved symptom burden of heart failure.

Of note, although there was a significant reduction in hsCRP levels, only 2 patients achieved on-treatment hsCRP <2 mg/L (which is considered the upper limit of normal). In CANTOS (Canakinumab Antiinflammatory Thrombosis Outcome Study), a recently published trial of IL-1 blockade in patients after myocardial infarction, overall rates of composite cardiovascular events were reduced with canakinumab, a monoclonal antibody to IL-1β (10), especially in those patients who achieved hsCRP levels <2.0 mg/L (11). Thus, in addition to being hindered by a small sample size, this study may have been underpowered to detect changes in surrogate markers of improved clinical status (cardiopulmonary exercise testing parameters) because of a failure to achieve the desired degree of inflammatory suppression. Whether this could be solved by longer treatment, higher doses of anakinra, or an alternative agent is uncertain. A larger study, ideally one that is longer in treatment duration as well as randomized and placebo controlled, is needed to further expand on these findings and explore the potential role of IL-1 blockade in PAH with RV failure. ■

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

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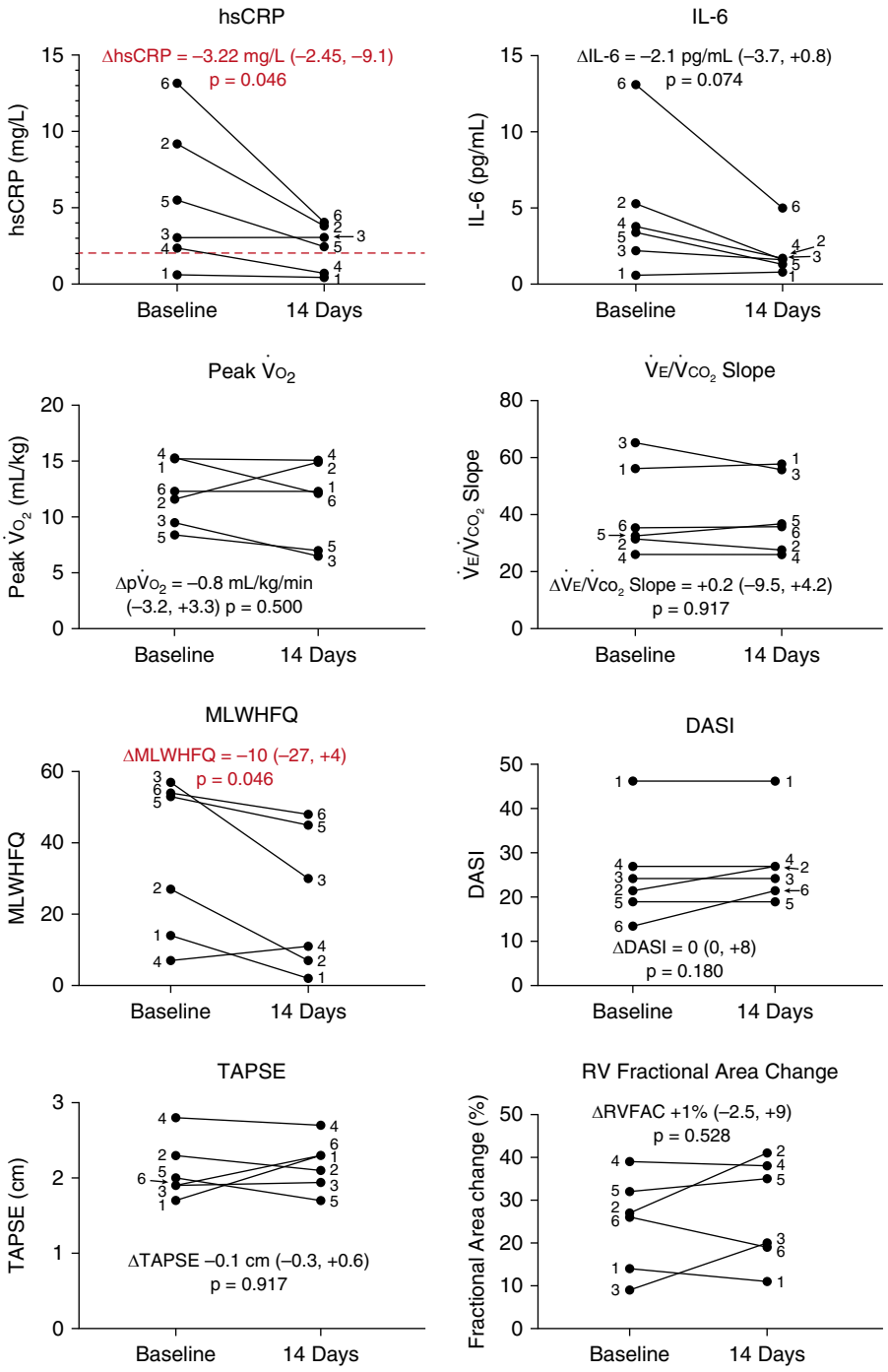

Figure 1. Study results. DASI = Duke Activity Severity Index; hsCRP = high-sensitivity C-reactive protein; MLWHFQ = Minnesota Living with Heart Failure Questionnaire; pV̇O2 = peak V̇O2; RV = right ventricular; RVFAC = RV fractional area change; TAPSE = tricuspid annular plane systolic excursion.

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Electrical Impedance Tomography Can Identify Ventilation and Perfusion Defects: A Neonatal Case

To the Editor:

The interaction between ventilation and lung perfusion is fundamental for effective gas exchange. Increasingly, clinicians are seeking to understand ventilation–perfusion matching at the bedside. Electrical impedance tomography (EIT) is emerging as the most promising bedside tool to define regional ventilation, being noninvasive and radiation free and offering continuous monitoring across different clinical environments (1). The ability to determine lung perfusion at the bedside is limited, especially in infants. EIT can measure the heartbeat-related impedance signal within the chest and has been proposed as a method of also defining regional lung perfusion (1–3). Unlike the impedance signal during ventilation, the cardiac signal is of lower amplitude and occurs at a faster and more variable rate. This, and a lack of a true biological model, has limited validating EIT measures of lung perfusion.

Herein we report the case of a 13-day-old infant born with an antenatal complete left pulmonary artery thrombosis and infarction of the left lung. This resulted in an almost complete absence of ventilation and perfusion in the left lung and a normal right lung. This provides a unique natural biological model in which to determine the role of perfusion and direct cardiac movement within the heartbeat-related signal generated during EIT.

Case Report

A 34-weeks' gestation male infant (birth weight, 2,720 g; Apgar score, 8 and 8 at 5 and 10 min) developed tachypnea and 25% oxygen requirement over the first 6 hours of life requiring continuous positive airway pressure in a regional hospital. He did not require any respiratory intervention at birth. An initial chest radiograph demonstrated complete consolidation of the left lung with extensive air bronchograms and a normal right lung (Figure 1A). The infant was transferred to the regional neonatal intensive care unit of the Royal Children's Hospital (Melbourne, Australia) for further management. Respiratory symptoms improved and continuous positive airway pressure was ceased on Day 3 of life. Chest computerized tomogram on Day 8 of life demonstrated complete occlusive thrombosis at the origin of the left pulmonary artery with extensive distal propagation and infarction of the left lung (Figure 1B). Further ultrasound imaging confirmed no structural heart disease and identified a left renal artery thrombosis and left adrenal thromboembolic infarct. Central nervous system imaging, including vessels, was normal. Intravenous heparin (until Day 10) and ongoing enoxaparin were administered.

EIT Methods

After obtaining informed written parental consent, EIT measurements were recorded on Day 13 at 48 scans during four 10-minute intervals of quiet unsupported breathing (no respiratory support) in a supine position using our previously detailed methods (Pioneer-Set with LuMon belt; Swisstom AG) (4). EIT images were reconstructed using the vendor-provided human model atlas with thoracic shape and lung and heart regions defined from a collection of computed tomography images. The image sequence was separated into heartbeat- and ventilation-related components by ensemble averaging. End-inspiratory peaks were detected in the average signal in the lung regions, and peaks corresponding approximately to systole were detected in the average heart-region signal. EIT pixel waveforms were aligned at each peak and averaged to create ventilation- and cardiac-synchronized components, and functional images were calculated corresponding to the times at which the maximum change in the lung regions occurred. Heartbeat-related EIT signals in the lungs and heart are normally out of phase, and the inverse conductivity change is not shown (primarily in the heart region).

EIT Results

Figure 2A shows representative impedance time course signals for the right and left lung and heart regions from a 45-second recording containing 32 consecutive breaths and 87 heartbeats. The mean total tidal volume was distributed as 93:7 between the right and left lung (Figure 2B). Similarly the right:left heartbeat-related signal within the lung regions was distributed as 81:19 (Figure 2C).

Discussion

This case provides a unique biological model to investigate the ability of EIT to define regional ventilation–perfusion patterns. Currently, ventilation–perfusion matching in infants is rarely determined because of the difficulties obtaining images outside of

Supported by National Health and Medical Research Council Clinical Career Development Fellowship grant 1053889 (D.G.T.) and the Victorian Government Operational Infrastructure Support Program, Melbourne, Australia (D.G.T. and S.R.).

Author Contributions: D.G.T. and S.R. obtained the imaging data and provided clinical interpretation. A.D.W., I.F., and A.A. performed the electrical impedance tomography analysis. D.G.T. wrote the first draft, and all authors contributed to redrafting the manuscript.

Originally Published in Press as DOI: 10.1164/rccm.201808-1551LE on October 26, 2018