165

Hyperpolarized xenon gas ventilation magnetic resonance imaging detects lung ventilation improvement in children with cystic fibrosis treated with elexacaftor/tezacaftor/ivacaftor in a multisite study

L. Walkup[1,2], D. Roach[1], B. Zanette[3], G. Santyr[3], S. Fain[4], M. Rock[5], J. Mata[6], D. Froh[7], S. Stanojevic[8], F. Ratjen[3,9], J. Woods[1]. *[1]Pulmonary Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [2]Biomedical Engineering, University of Cincinnati, Cincinnati, OH; [3]Translational Medicine Program, SickKids Research Institute, Hospital for Sick Children, Toronto, Ontario, Canada; [4]Radiology, University of Iowa, Iowa City, IA; [5]Pediatric Pulmonology and Sleep Medicine, University of Wisconsin, Madison, WI; [6]Radiology and Medical Imaging, University of Virginia, Charlottesville, VA; [7]Pediatric CF Program, University of Virginia, Charlottesville, VA; [8]Community Health and Epidemiology, Dalhousie University, Halifax, Nova Scotia, Canada; [9]Division of Respiratory Medicine, Department of Paediatrics, Hospital for Sick Children, Toronto, Ontario, Canada*

Background: Hyperpolarized xenon gas ventilation magnetic resonance imaging (Xe-MRI) assesses regional airflow and ventilation heterogeneity in obstructive lung diseases. Xe-MRI can detect early airflow obstruction in people with cystic fibrosis (CF) with normal spirometry, and its primary outcome measure, Xe ventilation defect percentage (VDP), correlates with the lung-clearance index (LCI), a measure of global ventilation inhomogeneity [1]. Xe-MRI is a promising outcome measure for trials of new therapies in CF and airway disease, but data in a multicenter setting assessing treatment response are lacking. We hypothesized that Xe-MRI would be sensitive to elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) treatment response in children with CF.

Methods: As part of the ongoing HyperPOlarized Imaging for New Treatments (HyPOINT) study, 19 children with CF (9 male, 10 female; mean age 12 ± 3) across four sites were assessed at two study visits: baseline and 30 ± 14 days after clinical initiation of ELX/TEZ/IVA. Coronal xenon ventilation images were acquired with a resolution of 3 × 3 × 15 mm^3 using a two-dimensional gradient-echo sequence at 3 Tesla with a xenon gas mixture dosed at 1/6th predicted total-lung capacity and breath-hold duration of 16 seconds or less. Xe-VDP was measured using a semi-automated segmentation, with defects defined as voxels with signal less than 60% of the mean whole-lung xenon signal and quantified as a percentage of whole-lung volume. Medians and interquartile ranges (IQRs) were used to describe VDP and percentage predicted forced expiratory volume in 1 second (FEV_1pp), with changes after ELX/TEZ/IVA assessed using Wilcoxon signed-rank tests. Spearman correlation was used to assess the relationship between changes in VDP and FEV_1. VDP improvement was defined as a 2% or greater decrease [2].

Results: Baseline median VDP (10.3%, IQR 5.7–17.5%) improved to 6.5% (IQR 2.9–12.2%) with ELX/TEZ/IVA ($p < 0.001$; Figure 1A). Median change in VDP was –2.4% (IQR –7.2 to –0.5%). Baseline median FEV_1pp (87%, IQR 71–100%) increased to 99% (IQR 78–107%) with ELX/TEZ/IVA ($p = 0.02$; Figure 1B). Median change in FEV_1pp was 6% (IQR 4–12.6%). Change in FEV_1 had a negative correlation with change in VDP ($r = –0.652$, $p = 0.002$; Figure 1C. Eleven of 19 (58%) participants had an improvement in VDP of 2% or more with ELX/TEZ/IVA.

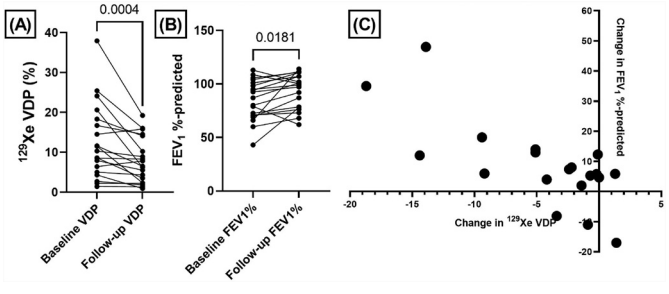

Figure 1. (A) Hyperpolarized xenon gas ventilation defect percentage (Xe-VDP) and (B) percentage predicted forced expiratory volume in 1 second (FEV_1pp) changes after elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) therapy. (C) Changes in FEV_1pp versus changes in VDP with ELX/TEZ/IVA therapy.

Conclusions: Ventilation improvement was observed with Xe-MRI after approximately 30 days of ELX/TEZ/IVA in a cohort of children with CF. Changes in VDP correlated with FEV_1, an established outcome for CF interventional trials. Xe-MRI detected ventilation improvement in patients who did not have change in FEV_1. Ongoing work will compare these short-term Xe-MRI changes with LCI and other clinical outcomes as the HyPOINT study continues to assess sustainability of therapeutic response for Xe-MRI, pulmonary function measures, and clinical outcomes 6 and 12 months after ELX/TEZ/IVA therapy initiation.

Acknowledgements: This work was supported by the Cystic Fibrosis Foundation (WOODS19A0). This abstract is presented on behalf of the HyPOINT study team.

References

[1] Kanhere N, Couch MJ, Kowalik K, Zanette B, Rayment JH, Manson D, *et al. Am J Respir Crit Care Med* 2017;196(8):1073–5. https://doi: 10.1164/rccm.201611-2228LE.

[2] Eddy RL, Svenningsen S, McCormack DG, Parraga G. *Eur Respir J* 2018;51:1800324. https://doi: 10.1183/13993003.00324-2018.

166

Measuring adherence to chronic therapies over the first year of treatment with elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis

S. Sutton[1,2], J. Hayden[2], M. Howlett[1,2], J. Davies[3,4,5], A. Fleming[6], B. Elnazir[7,8], M. Williamson[1], E. McKone[9,10], D. Cox[10,11], B. Linnane[12], A. Quittner[13], P. McNally[14]. *[1]Pharmacy, Children's Health Ireland at Crumlin, Dublin, Ireland; [2]Pharmacy, Royal College of Surgeons Ireland, Dublin, Ireland; [3]Department of Paediatric Respiratory Medicine, Royal Brompton Hospital, Guys and St. Thomas's NHS Foundation Trust, London, UK; [4]National Heart and Lung Institute, Imperial College, London, UK; [5]European Cystic Fibrosis Society, Lung Clearance Index Core Facility, London, UK; [6]Royal College of Surgeons Ireland, Dublin, Ireland; [7]Paediatric Respiratory Medicine, Children's Health Ireland, Dublin, Ireland; [8]School of Medicine, Trinity College, Dublin, Ireland; [9]Respiratory, St Vincent's University Hospital, Dublin, Ireland; [10]School of Medicine, University College Dublin, Ireland; [11]Respiratory, Children's Health Ireland, Dublin; [12]School of Medicine, University of Limerick, Limerick, Ireland; Paediatric Respiratory, University Hospital Limerick, Limerick, Ireland; [13]Behavioral Health Systems Research, Miami, FL; [14]Research and Innovation, Children's Health Ireland, Dublin; School of Medicine, Royal College of Surgeons Ireland, Dublin, Ireland*

Background: RECOVER is a multisite (n = 8) post-marketing real-world study of clinical outcomes in people with cystic fibrosis (CF) prescribed elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) across Ireland and the United Kingdom. Potential decline in adherence to chronic CF treatments in people on ELX/TEZ/IVA is unknown, which is considered a significant knowledge gap.

Methods: Adherence will be assessed using three methods: medication possession ratio (MPR) from pharmacy refill data, self-reported questionnaires (SRQ) [Treatment adherence questionnaire (TAQ) and Adherence Barriers Questionnaire (ABQ)], and the electronic Medication Electronic Monitoring System (MEMS). Information from self-report tools and pharmacy refills was collected for all participants. MEMS was used to measure adherence to ELX/TEZ/IVA in a subset of participants.

Results: One hundred sixteen participants aged 12 and older have been recruited. Available baseline and 12-month MPR data (n = 20) have shown suboptimal adherence for dornase alpha (59%, 48%, $p = 0.24$), hypertonic saline (63%, 47%, $p = 0.21$), azithromycin (69%, 33%, $p = 0.07$), and pancreatic enzymes (10,000 units 62%, 54%, $p = 0.65$; 25,000 units 54%, 51%, $p = 0.79$). Adherence to ELX/TEZ/IVA (95%, 99.7% $p = 0.01$) was greater. Available baseline and 12-month data from TAQ (n = 30) also indicated substandard adherence for modulators (100%, 89%, $p = 0.169$), dornase alpha (79%, 62%, $p = 0.27$), hypertonic saline (77%, 52%, $p = 0.18$), airway clearance (72%, 51%, $p = 0.05$), azithromycin (84%, 80%, $p = 0.78$), and pancreatic enzymes (100%, 100%, $p = 1$). Initial recruitment for MEMS was high (n = 32/40, with 15/32 (47%) remaining at 12 months). MEMS data indicated adherence rates of 82.7% for ELX/TEZ/IVA (n = 9) and 83.1% for ivacaftor (n = 9), for overall adherence of 82.9% (Figure 1).

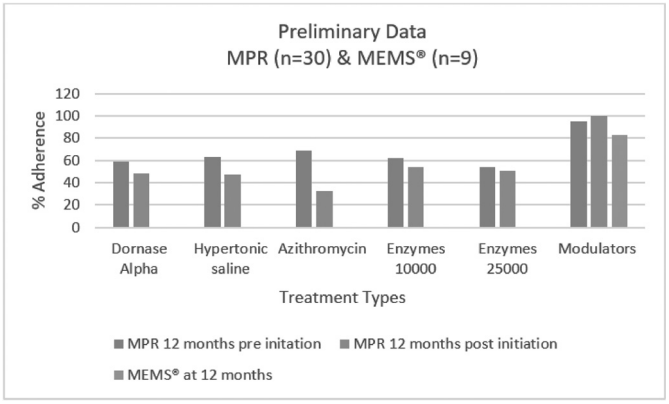

Figure 1. Preliminary medication possession ratio (MPR) data before and after introduction of elexacaftor/tezacaftor/ivacaftor and Medication Electronic Monitoring System (MEMS) data for overall adherence at 12 months

Conclusions: ELX/TEZ/IVA adherence may be overestimated in SRQ and MPR data. Adherence to routine CF therapies is poor, and initiation of ELX/TEZ/IVA may contribute to further reductions with some treatments. Data collection is ongoing for this cohort. Additional data will be available for presentation at the conference.

167

Two-year respiratory culture and pulmonary function outcomes in patients on elexacaftor/tezacaftor/ivacaftor

Z. Holliday[1]. [1]*Internal Medicine, University of Missouri, Columbia, MO*

Background: Elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA), a combination cystic fibrosis (CF) transmembrane conductance regulator modulating medicine, has been widely available to patients in the United States for the past 2 to 3 years. Multiple studies have reflected the improvement in respiratory symptoms and measurements that clinicians have noted while caring for these patients. Previous modulator therapies found similar improvements in respiratory measurements, yet patients were found to have return of baseline *Pseudomonas aeruginosa* densities at 2 years [1]. We investigated whether similar findings would occur with ELX/TEZ/IVA therapy after 2 years and whether improvements in pulmonary function testing measurements would persist as well.

Methods: A retrospective, single-center study was performed using patient data from the adult CF program at the University of Missouri. Fifty patients were included in the analysis, with each patient having completed a pulmonary function test and respiratory culture before and after starting therapy with ELX/TEZ/IVA and again approximately 2 years later.

Results: Significant improvement was found in percentage predicted forced expiratory volume in 1 second (FEV_1pp), percentage predicted forced vital capacity (FVCpp), and absolute change in forced expiratory volume in 1 second (FEV_1 L) and forced vital capacity (FVC L) soon after starting ELX/TEZ/IVA, as well as continued improvement at 2 years in FEV_1pp (mean difference 95% CI, 0.24–5.75, $p = 0.03$) and FVCpp (mean difference 95% CI, 2.6–7.76, $p < 0.001$). There was a significant reduction in percentage of positive respiratory cultures for *P. aeruginosa* soon after starting ELX/TEZ/IVA that persisted at 2 years (mean difference 95% CI, −3.05 to −32.95, $p = 0.01$) (Figure 1A). Unlike *P. aeruginosa*, the percentage of positive respiratory cultures for *Staphylococcus aureus* was not significantly different soon after starting therapy but was found to be significantly lower at 2 years (mean difference 95% CI, −12.5 to −43.5, $p < 0.001$) (Figure 1B). Like *S. aureus*, a significant reduction in percentage of positive respiratory cultures for *Aspergillus* species was found at 2 years that was not seen right after starting therapy (mean difference 95% CI, −2.02 to −25.98, $p = 0.02$) (Figure 1C). No significant difference was noted at 2 y ears in cultures positive for *Candida* species after starting ELX/TEZ/IVA, although a trend toward significance was found at 2 years despite most cultures being obtained via throat swab cultures (before vs 2 years, mean difference 95% CI 3.5 to −39.5, $p = 0.12$) (Figure 1D).

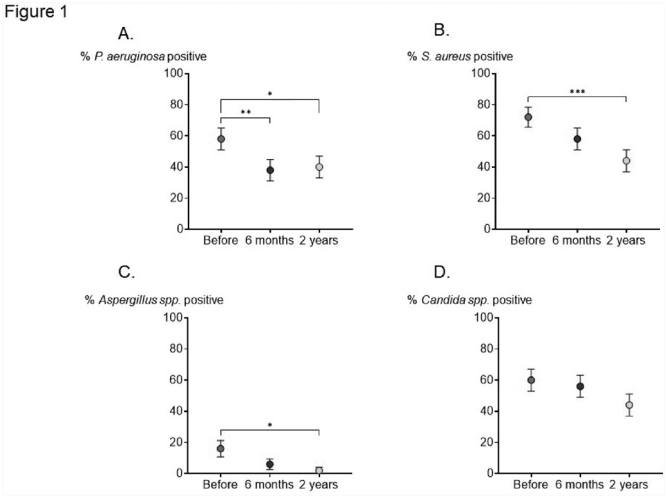

Figure 1. Percentage of respiratory cultures positive for (A) *Pseudomonas aeruginosa,* (B) *Staphylococcus aureus,*(C) *Aspergillus* spp., and (D) *Candida* spp. before, 6 months after, and 2 years after starting elexacaftor/tezacaftor/ivacaftor

Conclusions: Unlike previously seen return-to-baseline bacterial colonization densities at 2 years with early modulator therapies, patients at our center continue to have a reduction in percentage positive respiratory cultures for *S. aureus*, *P. aeruginosa* and *Aspergillus* species 2 years after starting ELX/TEZ/IVA. Continued improvement in pulmonary function testing measurements were also found at 2 years, warranting further investigation.

Reference

[1] Kidd T. Pseudomonas aeruginosa infection after CFTR restoration. One step back, one step forward. *Am J Respir Crit Care Med* 2017;195:1550–1552.

168

Results from APPLAUD phase 2 study with pro-resolution drug candidate LAU-7b in adults with cystic fibrosis

M. Konstan[1,2], D. Polineni[3], J. Chmiel[4], L. Bilodeau[5], P. Middleton[6], E. Matouk[7], J. Houle[8], R. Pislariu[8], P. Colin[8], I. Kianicka[8], D. Potvin[9], D. Radzioch[10,11,12], L. Lands[13]. [1]*Case Western Reserve University, Cleveland, OH;* [2]*Rainbow Babies and Children's Hospital, Cleveland, OH;* [3]*Pulmonary and Critical Care Medicine, University of Kansas Medical Center, Kansas City, KS;* [4]*Department of Pediatrics, Indiana University School of Medicine, Indianapolis, IN;* [5]*Institut Universitaire de Cardiologie et de Pneumologie de Québec-Université Laval, Québec, Canada;* [6]*Westmead Clinical School, University of Sydney, Westmead, New South Wales, Australia;* [7]*Department of Medicine, McGill University, Montreal, Québec, Canada;* [8]*Laurent Pharmaceuticals, Inc., Montreal, Québec, Canada;* [9]*Excelsus Statistics Inc, Montreal, Québec, Canada;* [10]*Institute of Molecular and Translational Medicine, Palacky University, Olomouc, Czech Republic;* [11]*Faculty of Medicine, McGill University, Montreal, Québec, Canada;* [12]*Research Institute, McGill University Health Centre, Montreal, Québec, Canada;* [13]*Department of Pediatric Respirology, Montreal Children's Hospital, Montréal, Québec, Canada*

Background: LAU-7b (oral fenretinide) is a novel drug candidate that acts on membrane lipids to modulate inflammation signaling and protein trafficking. Membrane lipid imbalance is believed to play a role in aberrant pulmonary inflammation in individuals with cystic fibrosis (CF), leading to irreversible lung damage over time. Fenretinide was shown to correct the levels of certain membrane phospholipids and sphingolipids in multiple in vitro and in vivo models of CF, improving resolution of inflammation and increasing functional CFTR expression, even under cellular stress conditions. A phase 2 clinical trial (APPLAUD) was conducted in adults with CF to evaluate the safety of LAU-7b and its effect on preservation of lung function by reducing inflammation and restoration of homeostasis.