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.

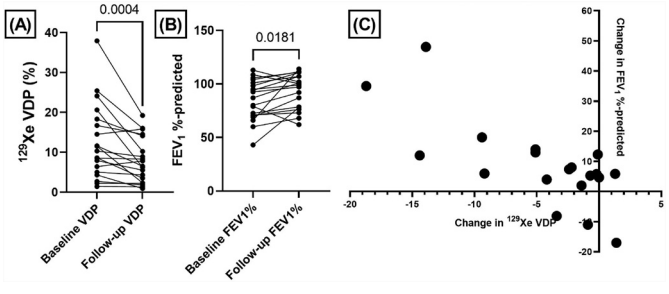

Figure 1. (A) Hyperpolarized xenon gas ventilation defect percentage (Xe-VDP) and (B) percentage predicted forced expiratory volume in 1 second (FEV_1pp) changes after elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) therapy. (C) Changes in FEV_1pp versus changes in VDP with ELX/TEZ/IVA therapy.

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).