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Reply to Kalverda *et al.*

From the Authors:

We thank Kalverda and colleagues for their letter regarding our recently published paper (1), and we appreciate the opportunity to provide additional clarity on the points they raise about the work. Below we address the questions asked by Kalverda and colleagues.

This study was funded in part by the NIH (grant numbers K23HL132120, R01HL152075, and P41EB015903), an investigator-initiated study (IIS) grant from Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI), and the LUNGevity Foundation. BIPI had no role in the design, analysis, or interpretation of the results of this study. Boehringer Ingelheim was given the opportunity to review the manuscript for medical and scientific accuracy as it relates to BIPI substances, as well as intellectual property considerations.

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Enrollment Criteria

Our primary objective was to conduct a blinded, prospective study to evaluate the diagnostic accuracy of endobronchial optical coherence tomography (EB-OCT) for microscopic diagnosis of interstitial lung disease (ILD) compared with concurrent surgical lung biopsy (SLB) and clinical follow-up diagnosis. Our inclusion criteria were *1*) age > 21 years; *2*) fibrotic ILD on the basis of high-resolution computed tomography (HRCT) with unclear diagnosis; *3*) SLB required for ILD diagnosis on the basis of the clinical decision of the treating pulmonologist, and *4*) ability to give informed consent. Therefore, in our patient cohort, there was no high-confidence clinical-radiologic diagnosis before SLB. Our institution does not routinely use BAL as part of the ILD diagnostic workup, which is consistent with the practice of many academic ILD centers in the United States. The clinical follow-up diagnosis for each patient was determined by the treating pulmonologist on the basis of clinical, HRCT, SLB, and serology data and was provided in Table 3 in our paper (1). Formal presentation in a multidisciplinary discussion conference was conducted after SLB as deemed necessary by the treating pulmonologist and was performed in ∼60% of the cases in our cohort.

EB-OCT Probe Placement in Subpleural Lung and Reproducibility

To reach the subpleural lung, the flexible EB-OCT catheter was advanced through the bronchoscope working channel and extended beyond the visualized region of the bronchoscope until resistance was met in the subpleural lung at each imaging site. This method for reaching the subpleural lung was developed and validated in our prior *ex vivo* studies of EB-OCT in whole explanted lungs, including lungs with end-stage ILD, using visual and tactile inspection to confirm subpleural catheter placement (2, 3). In the present *in vivo* study, fluoroscopy was performed in two subjects and also confirmed the subpleural location of the catheter in both cases (1). In this study, an individual with experience in EB-OCT interpretation was present during the procedure to confirm subpleural positioning of the EB-OCT catheter at the beginning of each scan and to ensure adequate data quality and sampling of anatomic sites for diagnosis. Occasionally, the catheter would hit a branchpoint, creating a sensation of resistance similar to that of the subpleural lung, but these instances were infrequent and readily recognizable during the intraprocedural adequacy assessment. This is reflected in our average time of 9.5 minutes per patient for EB-OCT imaging, which included the time needed for intraprocedural EB-OCT adequacy evaluation and instances requiring catheter repositioning. We did not perform repeat imaging in the same airway segment unless there was a need to reposition the catheter. We believe our ability to reach the correct anatomic location in the subpleural lung is reflected in our data, which demonstrated 100% sensitivity and specificity for histopathologic usual interstitial pneumonia (UIP) and strong agreement (weighted kappa = 0.87) with SLB for diagnosis of fibrotic ILD pattern.

We agree with Kalverda and colleagues that the described "subpleural sign" mentioned in their letter (4) is consistent with the appearance of pleura and chest wall tissues, which we have also seen in our EB-OCT imaging data. In our experience, we have found that the imaging angle of side-viewing EB-OCT catheters, such as the catheter used in our study, does not allow pleura and chest wall tissues to be within the imaging field of view in many anatomic locations within the lung (i.e., where the imaging beam is parallel to

the pleura and chest wall). Therefore, we did not find that this sign had utility as a reliable indicator of subpleural lung location.

Potential Use of Saline Flushing to Improve Imaging Quality

We did not use saline flushing during EB-OCT imaging in our study. We found in our prior *ex vivo* and *in vivo* studies that we were able to achieve high-resolution, diagnostic-quality imaging without the use of saline (2, 3) and thus opted to perform EB-OCT imaging without the use of saline flushing. We agree with Kalverda and colleagues that saline flushing would likely improve EB-OCT imaging quality by providing a closer index match between the tissue and alveolar spaces. However, this adds additional complexity and time to the procedure.

Image Interpretation and Training

We performed EB-OCT in each subject in multiple distinct airways in the upper, middle, and lower lung lobes (an average of six EB-OCT imaging sites per patient), which were selected on the basis of regions of abnormality seen on the most recent HRCT study. All EB-OCT readers interpreted all cross-sectional images from all EB-OCT imaging sites, using the criteria in Table 1 in our paper, to provide a single diagnosis per subject (1).

Three pathologists with expertise in ILD and no prior experience with OCT imaging (referred to as novice readers) were trained and tested on EB-OCT interpretation. After completion of the initial study analysis by the expert EB-OCT reader, the study data were divided into training and testing data sets (each comprising 50% of the study subjects, with equal proportions of each ILD diagnosis). The training requirement for the three novice EB-OCT readers was to undergo a 3-hour training session with the expert EB-OCT reader, which covered basic principles of EB-OCT and application of EB-OCT imaging criteria for the diagnosis of UIP and non-UIP ILD using subject cases from the training data set. After the training session, the novice EB-OCT readers were asked to independently evaluate the EB-OCT data for each subject in the testing data set, blinded to histopathology and other assessments of EB-OCT data by the expert and novice readers. Two of the novice EB-OCT readers achieved sensitivity and specificity of 100% for histopathologic UIP and clinical idiopathic pulmonary fibrosis. The EB-OCT imaging features correlate directly with histopathologic features, and thus we do not anticipate difficulty in training ILD pathology experts to identify other specific fibrotic ILD patterns in the future. However, as we discussed in the paper, this needs to be evaluated further in future, larger-scale studies.

Use of Polarization-Sensitive OCT in ILD

We agree with Kalverda and colleagues that polarization-sensitive OCT (PS-OCT), which is a modification to traditional OCT that simultaneously detects tissue birefringence from organized tissues such as collagen, could be of great benefit in the evaluation and quantification of fibrosis in ILD. Our group has significant experience with PS-OCT for assessment of lung fibrosis in the setting of lung cancer and smooth muscle in asthma (5–8). We have begun investigating the utility of PS-OCT in assessment of ILD, and our results to date have shown promise (9, 10).

Conclusions

We thank Kalverda and colleagues again for their interest in and appreciation of our research, and we congratulate them on their successful efforts investigating EB-OCT for ILD assessment. As we discussed in our paper, larger-scale multicenter studies will be essential to further validate our data on the diagnostic accuracy of EB-OCT in ILD assessment. We hope to establish collaborations with other interested ILD groups, as this will be an essential step preceding the potential implementation of EB-OCT in the clinical workflow. ■

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

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Global Initiative for Asthma 2021: Asthma in Preschool Children and Short-Acting β_2-Agonist–Only Treatment

To the Editor:

We read with interest the Global Initiative for Asthma (GINA) 2021 executive summary by Reddel and colleagues (1), which summarizes key recommendations for asthma management and the evidence underpinning recent changes. A landmark new recommendation for adolescents and children >6 years of age is that short-acting β_2-agonists (SABAs) be given in combination with inhaled corticosteroids (ICS) to reduce the risk of severe exacerbations and asthma-related death (2).

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